Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2001-09

Zoxamide
Zoxium® 80W Fungicide, Gavel® 75DF Fungicide

The active ingredient Zoxamide, and associated end-use products Zoxium® 80W Fungicide (containing the active ingredient Zoxamide) and Gavel® 75DF Fungicide, (containing the active ingredients Zoxamide and Mancozeb) for the control of downy mildew on grapes and late blight on potatoes, have been granted temporary registration under Section 17 of the Pest Control Products Regulations.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued temporary registrations for Zoxamide, a fungicide developed by Rohm and Haas Canada Inc. and the associated end-use products, Zoxium® 80W Fungicide (containing Zoxamide only) and Gavel® Fungicide 75DF, containing Zoxamide and the currently registered fungicide Mancozeb, for the control of downy mildew on grapes and late blight on potatoes. These products were reviewed jointly as reduced-risk (grapes) and nonredused-risk (potatoes) products within the North American Free Trade Agreement's Technical Working Group on Pesticides (NAFTA TWG) Joint Review Program by Health Canada's Pest Management Regulatory Agency and the US Environmental Protection Agency.

Methods for analysing Zoxamide in environmental media are available to research and monitoring agencies upon request to the PMRA.

Rohm and Haas Canada Inc. will be carrying out additional chemistry, toxicology, storage stability, environmental chemistry and value studies as well as a stewardship program as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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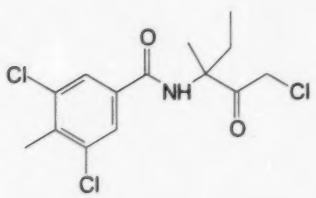
1.0 The active substance, its properties, and uses

1.1 Identity of the active substance and impurities

Active Substance:	Zoxamide
Function:	Fungicide
Chemical name:	
International Union of Pure and Applied Chemistry (IUPAC):	3,5-Dichloro-*N*-(3-chloro-1-ethyl-1-methylacetonyl)-*p*-toluamide
Chemical Abstracts Service (CAS):	3,5-Dichloro-*N*-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide
CAS number:	156052-68-5
Molecular formula:	$C_{14}H_{16}NO_2Cl_3$
Molecular weight:	336.65
Structural formula:	
Nominal purity of active:	98% (nominal) concentration of Zoxamide (full scale production will be 97% nominal).
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade Zoxamide does not contain any impurities or microcontaminants known to be Toxic Substances Management Plant (TSMP) Track-1 substances. No nitrosamines were detected and none would be expected in this product.

1.2 Physical and chemical properties of active substances and end use product(s)

Technical product

Property	Result	Comment
Colour and physical state	Fine white powder	
Odour	Licorice-like	

Property	Result	Comment
Melting point or range	159.5 - 161.0°C, with irreversible chemical change	
Boiling point or range	n/a	
Density Tap bulk density Pour density	1.38 at 20°C 0.498 g/mL 0.371 g/mL	
Vapour pressure at 25°C	1.52×10^{-7} Pa	Non-volatile under field conditions
Henry's law constant at 20°C	7.52×10^{-5} Pa m^3/mol	Non-volatile from water and moist soil
Ultraviolet (UV) - visible spectrum	Condition / λ max (nm) Neutral 212.0 241.2 Acidic 212.4 241.4 Alkaline 218.2 244.8	Not likely to phototransform at environmentally relevant wavelengths of light
Solubility in water at 20°C	0.681 ppm ± 0.017	Sparingly soluble
Solubility in organic solvents at 20°C	Solvent / g/L ethyl acetate 20.0 acetone 55.7 xylene 1.56 n-octanol 6.49 n-heptane 0.038 1,2-dichloroethane 12.5	
n-Octanol-water partition coefficient	log K_{ow} = 3.76 ± 0.04	Low potential for bioaccumulation
Dissociation constant	pK_a could not be determined due to low water solubility	
Stability (temperature, metal)	Stable at elevated heat and pressure alone and with added 316 L stainless steel, carbon steel, iron II or iron III	

End-use product: Zoxium® 80W Agricultural Fungicide

Property	Result
Colour	Tan to light gray
Odour	Faint sweet
Physical state	Powder
Formulation type	Wettable powder (WP)

Property	Result
Guarantee	80% nominal
Formulants	The product does not contain any EPA List 1 formulants or formulants known to be TSMP Track-1 substances.
Container material and description	Plastic lined paper bag
Bulk density	Bulk density 0.22 g/mL, loose 0.30 g/mL, packed
pH of 1% dispersion in water	8.8
Oxidizing or reducing action	None of the components was an oxidizing or reducing agent.
Storage stability	Stable after 2 weeks at 54°C in commercial or similar container. One year storage stability data expected in 2001
Explodability	Not considered explodable

1.3 Details of uses

The new active ingredient Zoxamide causes the disruption of the microtubule cytoskeleton and arrests nuclear division by binding specifically to tubulin. Two commercial end-use products containing Zoxamide have been reviewed for registration, Zoxium® 80W Fungicide, a WP containing 80% Zoxamide, and Gavel® 75DF Fungicide, a DF containing 8.3% Zoxamide and 66.7% Mancozeb. Zoxium® 80W Fungicide is being registered as a tankmix application with Dithane® DG Rainshield NT Fungicide (Mancozeb) for control of late blight and early blight on potatoes and applied alone for control of downy mildew on grapes. For additional control of powdery mildew and black rot on grapes, Zoxium® 80W Fungicide can be tankmixed with Nova® 40W Fungicide (Myclobutanil). Gavel® 75DF Fungicide is being registered for control of late blight and early blight on potatoes and downy mildew on grapes.

2.0 Methods of analysis

See Appendix III for summary tables.

2.1 Methods for analysis of the active substance as manufactured

The active was determined using a high performance liquid chromatographic (HPLC) method. Related impurities (>0.1%) were determined by gas chromatography (GC) and HPLC methods. The methods were satisfactorily validated.

2.2 Method for formulation analysis

A fully validated HPLC method was used for the determination of active substance in Zoxium® 80W Agricultural Fungicide and Gavel 75DF Agricultural Fungicide. Mancozeb in Gavel 75DF Agricultural Fungicide was determined by a CS_2 evolution

method. This is the only method available for determination of Mancozeb and was considered acceptable.

2.3 Methods for residue analysis

ANALYTICAL METHODS: PLANT AND ANIMAL MATRICES
GC with electron capture detector (GC-ECD) and GC with mass selective detection (GC-MSD)
Residue of concern (ROC): residue of Zoxamide per se
3,5-dichloro-N-(3-chloro-1-ethyl-1-methylacetonyl)-p-toluamide in grapes and the combined residues of Zoxamide and its metabolites 3,5-dichloro-1,4-benzenedicarboxylic acid (designated by company code RH-141455 or RH 1455) and 3,5-dichloro-4-hydroxymethyl benzoic acid (RH-141452 or RH-1452) in potato

Matrix	Grape					
	grape	juice	raisins			
Limit of quantitation (LOQ)	0.01	0.01	0.01			
Recovery: mean (%) ± SD	91.5±15.8	average 109	average 107			
Matrix	potato (sum of three metabolites)					
	tuber	flakes	chips	peel		
Limit of quantitation (LOQ)	0.06	0.06	0.06	0.06		
Recovery: mean (%) ± STDEV	81.5 - 92.3 ±13.3 - 19	103 ± 13	93.2 ± 9.9	87 - 127		
Matrix	Dairy cattle & Poultry					
	Milk	Lean meat	Fat	Eggs	Liver	Kidney
Limit of quantitation (LOQ)	No methods submitted					
Recovery: mean (%) ± SD	Not applicable					

3.0 Impact on human and animal health

See Appendix II for summary tables.

3.1 Integrated toxicological summary

Absorption, distribution, metabolism, and excretion
Zoxamide was rapidly and extensively absorbed, metabolized and excreted. Approximately 61% of the administered dose was systemically absorbed. Absorption was less complete in high dose groups. Plasma concentrations peaked approximately 8 h post dose. Residue concentrations were highest in organs associated with absorption (liver, stomach, intestines). Metabolism occurred by primary hydrolysis, glutathione mediated reactions and reductive dehalogenation; secondary oxidation of the aromatic methyl and the aliphatic side chain; and terminal glucurionic acid and amino acid conjugations.

Induction of metabolism (glutathione transferase and/or glutathione cofactor) appeared to occur. Elimination from plasma was bi-phasic with an elimination half-life of 12 - 14 h. No residues were detected in expired air. Altogether, in urine and faeces, 32 separate metabolites were identified; no single metabolite other than the parent accounted for more than 10% of the administered dose. Over 85% of the administered dose in single dose studies was excreted within 24- 48 h; the predominant route of excretion was hepatobiliary. No evidence of accumulation of the parent compound or its metabolites was observed. There were no apparent sex related differences.

The two major potato metabolites (RH-141452 and RH-141455), which were minor rat metabolites, were studied in separate metabolism studies. More than 97% of the administered dose (RH-141452) was excreted within 24 h. Greater than 94% was eliminated unchanged in urine. Two glucuronide conjugates and a glycine conjugate (~3% of the administered dose) were found in urine. An additional 1.6% of the administered dose was excreted unchanged in the feces. Excretion of RH-141455 was slower: 47% of the administered dose was excreted within 24 h, with an additional 32% of the administered dose excreted between 24 and 48 h. Greater than 92% of the administered dose was recovered (about 73% in feces, 11% in urine and 9% in cage rinse) as unchanged RH-141455 (>96%).

Mechanism of action

The anti-tubulin benzamide (ATB) compounds RH-117281 and RH-54032 inhibited nuclear division in the Oomycete fungus Phytophthora capsici by the disruption of cellular microtubules as the result of a highly specific covalent binding to the β-subunit of tubulin. In vitro microtubule assembly assays demonstrated an inhibition of assembly by RH-117281 and RH-54032, which was unusual in requiring a prolonged incubation with tubulin. RH-117281 was comparable in potency to carbendazim in inhibiting microtubule assembly and the growth of mouse lymphoma cells, and was considerably less active than colchicine and vinblastine. Consistent with whole cell labelling experiments, the binding of radiolabelled RH-54032 to isolated bovine tubulin was shown to involve the β-subunit. Non-specific binding, assumed to be covalent due to assay conditions, however, was shown to bind to other proteins in the mouse lymphoma cell assay. Since binding of radiolabelled RH-54032 to isolated tubulin was strongly inhibited by colchicine, podophyllotoxin and nocodazole, but not by vinblastine, it appears likely that the ATBs bind at or near the colchicine binding site of tubulin.

Acute toxicity

Technical Zoxamide, purity 98%, was considered to be of low acute toxicity by the oral, dermal and inhalation routes in CDBR rats (oral lethal dose 50% [LD_{50}] >5.0 g/kg bw; dermal LD_{50} >2.0 g/kg bw; inhalation lethal concentration 50% [LC_{50}] >5.0 mg/L) and by the oral route in CD-1 mice (oral LD_{50} >5.0 g/kg bw). It was non irritating when applied to the skin, but mildly irritating to eyes of New Zealand White (NZW) rabbits. Results of skin sensitization testing using guinea pigs, employing the Buehler and Maximization methods, indicated that the technical material was a strong dermal sensitizer.

The acute oral toxicity of two major potato metabolites (RH-141452 and RH-141455), which were minor rat metabolites, were studied in separate acute oral toxicity studies in the CD-1 mouse. The observed oral LD_{50} for both metabolites was greater than 5000 mg/kg bw.

The Zoxium® 80W Fungicide formulation, containing 80% Zoxamide, was considered to be of low acute toxicity by the oral, dermal and inhalation routes in CDBR rats (oral and dermal LD_{50} >5.0 g/kg bw; inhalation LC_{50} >3.8 mg/L). It was moderately irritating when applied to the skin of NZW rabbits, and was minimally irritating when instilled into the eyes of the same species. Results of skin sensitization testing in guinea pigs, employing the Buehler method, were positive.

The formulants were on EPA List 3 or 4B, and/or the Canadian Registered Products List, and were considered acceptable for use.

The Gavel 75DF formulation, containing 66.7% Mancozeb and 8.3% Zoxamide, was considered to be of low acute toxicity by the oral, dermal and inhalation routes in CDBR rats (oral and dermal LD_{50} >5.0 g/kg bw; inhalation LC_{50} >5.1 mg/L). It was minimally irritating when applied to the skin of NZW rabbits, and was minimally irritating when instilled into the eyes of the same species. Results of skin sensitization testing in guinea pigs, employing the Buehler method, were positive.

The formulants were on EPA List 3, 4A, or 4B, and/or the Canadian Registered Products List, and were considered acceptable for use.

Short- and long-term toxicity

A short-term dermal study showed strong skin irritation and evidence of a systemic immune response in all of the test groups after repeated applications of Zoxamide to the shaved skin of albino rats. The no observable adverse effect level (NOAEL) was not determined, and the lowest observable adverse effect level (LOAEL) was < 150 mg/kg bw/day. Clinical signs included scabbing. Treated skin showed hyperplasia, hyperkeratosis and inflammation. Other observations in the dermis consisted of hyperplastic sebaceous glands, mixed inflammatory cell infiltrations (mononuclear and polymorphonuclear leukocytes) and vasculitis and/or peri-vasculitis in the deeper dermis. The peri-vasculitis and vasculitis affected small to medium sized vessels and was characterized by the infiltration of mononuclear and polymorphonuclear inflammatory cells into the vessel wall and peri-vascular areas. Since the technical material was not a dermal irritant in acute studies, this reaction likely represents a dermal sensitization reaction.

In subchronic (90-day, one year) and chronic dietary studies, Zoxamide showed little evidence of toxicity below limit doses (1000 mg/kg bw/d). Dogs were the most sensitive species. In most studies where an effect was observed, females appear to be more sensitive. In a 90-day study, Zoxamide affected the liver in dogs, producing liver weight increases at 322 mg/kg bw/d, and in addition, liver hepatocellular hypertrophy, slight reductions in serum albumin levels, and slight thyroid follicular cell hypertrophy at

1055 mg/kg bw/d (limit dose). Following one year of treatment in dogs at similar doses, similar effects were noted on liver weights, hepatocellular hypertrophy, serum albumin and thyroid weights. In addition, serum alkaline phosphatase (ALP) was significantly increased, indicating some toxicity to the hepatobiliary system. These observations represent a progression from adaptive change associated with metabolism and detoxification of the compound to slight toxicity following one year of treatment at a limit dose of 1000 mg/kg bw/d. There was no indication of a target organ in either rats or mice. The NOAEL values in the 90-day mouse, rat and dog studies were ≥1666, ≥1509, and 62 mg/kg bw/d, respectively, and, in the 12 month dog study, 48 mg/kg bw/d.

Long-term studies in both rats and mice provided no evidence of treatment-induced oncogenicity at any dose level tested. The NOAEL for chronic toxicity and oncogenicity was set at the highest dose tested in both mice and rats: 1289 mg/kg bw/d and 1331 mg/kg bw/d, respectively.

Genotoxicity

No evidence of mutagenic potential of technical Zoxamide was observed *in vitro* with the Ames Bacterial Mutation Test, with and without metabolic activation. Under the conditions of an *in vitro* mammalian cell gene mutation assay (cultures of normal ($HGPRT^+$) Chinese hamster ovary (CHO) cells), technical Zoxamide was considered non-mutagenic for point mutations, frame-shift mutations and deletions. Zoxamide, when tested in a CHO assay with and without metabolic activation, did not show clastogenic potential. An increased incidence of numerical chromosomal aberrations was observed, with and without metabolic activation. In an *in vivo* study, however, technical Zoxamide did not induce micronuclei in a mouse micronucleus assay, indicating that the *in vitro* observation of numerical chromosomal aberrations was not of concern. In a supporting study, Zoxamide equivalents were shown to distribute to mouse bone marrow in concentrations peaking at 55 ppm. Based on the data presented, technical Zoxamide was not considered to be genotoxic under the conditions of the tests performed.

The two major potato metabolites of Zoxamide (RH-141452 and RH-141455) were tested for mutagenic potential with the Ames Bacterial Mutation Test. No evidence of mutagenic potential of technical Zoxamide was observed *in vitro* with this test, with and without metabolic activation.

Developmental and reproductive toxicity

Rat and rabbit developmental toxicity studies and a two-generation rat reproduction study indicated that Zoxamide was not teratogenic or a reproductive toxicant. No treatment related effects were noted in either the teratogenicity studies or the reproduction study at doses at or exceeding the limit dose (1000 mg/kg bw/d). The developmental toxicity NOAEL for both rat and rabbit was ≥1000 mg/kg bw/d. The rat reproductive toxicity NOAEL was ≥2091 mg/kg bw/d, while the dam systemic NOAEL was 409 mg/kg bw/d based on a slight body weight decrease during the pre-mating phase only.

Neurotoxicity

Acute and short-term (90-day) neurotoxicity studies conducted in the rat did not demonstrate any neurotoxic potential for Zoxamide. The acute neurotoxicity NOAEL was ≥1976 mg/kg bw, while the 90-day neurotoxicity NOAEL was ≥1509 mg/kg bw/d.

3.2 Determination of acceptable daily intake

The lowest NOAEL was in the one year dog study at a level of 48 mg/kg bw/d, based on treatment-related effects seen on the liver (increased weight, hepatocellular hypertrophy, decreased serum albumin, increased serum ALP) and an effect on the thyroid (increased weight, follicular cell hypertrophy) in both the 3- and 12-month dog studies. For the calculation of the acceptable daily intake (ADI), a safety factor (SF) of 100 is proposed. No additional safety or uncertainty factors are warranted.

The proposed ADI is calculated according to the following formula:

$$ADI = \frac{NOAEL}{SF} = \frac{48\ mg/kg\ bw/d}{100} = 0.48\ mg/kg/d\ of\ Zoxamide$$

3.3 Acute reference dose

An acute reference dose (ARfD) is not required since there was no indication of acute toxicity by the oral, dermal inhalation routes of exposure.

3.4 Toxicological end point selection: occupational and bystander risk assessment

Zoxamide was of low toxicity by all routes of exposure (dermal, oral, inhalation) in both acute and repeat dose studies. There was no evidence of carcinogenicity, neurotoxicity, developmental or reproductive toxicity, or increased sensitivity of the young, pre- or post-natally. Repeat dose studies in rats, mice and rabbits established NOAEL values at or above the limit dose of 1000 mg/ kg bw/d. The dog was more sensitive in repeat dose studies; NOAEL values of 62 and 48 mg/kg bw/d were established in 90-day and one-year studies, respectively. These NOAEL values were based on decreased feed consumption and body weight or body-weight gain and adaptive changes in the liver. There was no indication that toxicity increases with increased duration of exposure. There was no indication that any one route of exposure resulted in increased toxicity relative to other routes of exposure, and a route specific risk assessment is not required.

Based on the toxicity profile and the short- to intermediate- term duration of exposure, the NOAEL of 62 mg/kg bw/d was selected as most appropriate for the systemic occupational risk assessment. A margin of exposure (MOE) of 100 is considered adequate.

Technical Zoxamide is a moderate eye irritant and is not a skin irritant. Gavel® 75DF Fungicide is minimally irritating to both eyes and skin. Zoxium® 80W Fungicide is a moderate skin irritant and is minimally irritating to eyes. Technical Zoxamide is a strong

dermal sensitizer in both Buehler and Maximisation assays in the guinea pig. In addition, in a 28-day dermal toxicity study in the rat, a sensitization reaction was produced. Both end-use products are also dermal sensitizers.

As Zoxamide is a strong dermal sensitizer, it can be expected that a relatively higher incidence of sensitization could occur among exposed workers, compared with weak sensitizers. In addition, there is the potential that Zoxamide could present a sensitization hazard by the inhalation route of exposure. This concern is based on several observations: strength of dermal sensitization response; potential haptenation; inhalation allergic responses that can occur following sensitization via the dermal route. There is no information in the toxicology database to address this potential effect. At present there are no validated animal models for investigation of inhalation sensitization potential. Inhalation sensitization reactions can include rhinitis, alveolitis and asthma. Reactions can occur with higher incidence or severity in atopic individuals, i.e., those who are predisposed to allergic reactions.

3.5 Impact on human and animal health arising from exposure to the active substance or to its impurities

3.5.1 Operator exposure assessment

The end-use formulations, Zoxium® 80W Fungicide (a WP formulation containing 80% Zoxamide) and Gavel® 75DF Fungicide (a DF formulation containing 8.3% Zoxamide) are proposed for fungicidal use on potatoes and grapes. Application to potatoes may be by groundboom or aerial equipment. Application to grapes will be by airblast equipment. The maximum application rate of Zoxium® 80W Fungicide is 187 g-a.i./ha for potatoes (maximum six applications per season) and 224 g-a.i./ha for grapes (maximum eight applications per season). The maximum application rate of Gavel® 75DF Fungicide is 187 g-a.i./ha for both commodities (maximum six applications per season).

Dermal absorption
A dermal absorption study was conducted in male rats using a WP formulation similar to Zoxium® 80W Fungicide as well as a liquid flowable formulation. The WP formulation was deemed most relevant to both Zoxium® 80W Fungicide and Gavel® 75DF Fungicide. The derived absorption value after 10 h exposure was 8.8%. The study design did not permit analysis of the fate of skin bound residues (5.7%), which are therefore assumed to be available for absorption and included in the absorbed dose.

Exposure assessment
Based on the proposed use pattern (up to six to eight applications per season), both farmers and custom applicators are likely to be exposed intermittently over an intermediate time frame (i.e., the growing season).

Pesticide Handler's Exposure Database (PHED Version 1.1) assessments were conducted to derive estimates of occupational exposure for mixer, loaders and applicators wearing one layer of clothing, as well as gloves during mixing and loading. The PHED subsets

generally meet NAFTA criteria for PHED estimates and therefore provide an adequate basis for estimating occupational exposure for the proposed uses. PHED does not include data from which to estimate exposure during clean-up and repair activities and exposure potentially encountered during these activities is therefore not included in the estimates. Also, it is not possible to quantify the variability of PHED exposure estimates.

Based on the PHED exposure estimates and a dermal absorption value of 8.8%, exposure estimates were derived for the following scenarios:

- farmers mixing, loading and applying Zoxium® 80W Fungicide or Gavel® 75DF Fungicide for groundboom application to 65 ha potatoes per day at 0.187 kg a.i./ha

- custom operators mixing, loading and applying Zoxium® 80W Fungicide or Gavel® 75DF Fungicide for groundboom application to 400 ha potatoes per day at 0.187 kg a.i./ha

- mixing and loading Zoxium® 80W Fungicide or Gavel® 75DF Fungicide for aerial application to 400 ha potatoes per day at 0.187 kg a.i./ha

- aerially applying Zoxium® 80W Fungicide or Gavel® 75DF Fungicide to 400 ha potatoes per day at 0.187 kg a.i./ha

- farmers mixing, loading and applying Zoxium® 80W Fungicide for airblast to 20 ha grapes at 0.224 kg-a.i./ha

- farmers mixing, loading and applying Gavel® 75DF Fungicide for airblast to 20 ha grapes at 0.187 kg-a.i./ha

For Zoxium® 80W Fungicide, both inhalation and absorption through the skin are significant routes of exposure; the inhalation route contributes up to 60% of the total absorbed dose. Based on an analysis (provided by the applicant) of dispersed particle size of the Zoxium® 80W Fungicide formulation, up to 50% is inhalable to the alveolar region in humans. For Gavel® 75DF Fungicide, absorption through the skin is the primary route of exposure; the inhalation route contributes approximately 10-15% of the total absorbed dose. The vapour pressure of Zoxamide is very low and vapour exposure will be negligible.

MOE values based on total daily systemic exposure (absorbed dermal plus inhalation) and the NOAEL of 62 mg/kg bw/d from the 90-day dog toxicity study are shown below.

Exposure scenario	Zoxium® 80W Fungicide		Gavel® 75DF Fungicide	
	Daily Exposure[a] µg/kg bw/d	Margin of Exposure	Daily Exposure[a] µg/kg bw/d	MOE
Groundboom, farmer; mix, load and apply: potatoes 65 ha/d at 0.187 kg a.i./ha	23.3	2661	3.6	17222
Groundboom, custom applicator; mix, load and apply: Potatoes 400 ha/d at 0.187 kg a.i./ha	143	434	22	2818
Aerial, mix and load: potatoes 400 ha/d at 0.187 kg a.i./ha	138.2	449	17.2	3605
Aerial, apply: potatoes 400 ha/d at 0.187 kg a.i./ha	1.1	56364	11	5636
Airblast, mix, load and apply: grapes 20 ha at 0.187 kg a.i./ha	n/a	n/a	5.3	11698
Airblast, mix, load and apply: grapes 20 ha at 0.224 kg a.i./ha	13.6	4559	n/a	n/a

[a] Absorbed dermal + inhalation dose (assuming dermal absorption = 8.8% and inhalation absorption is equal to absorption through the gastrointestinal tract). Based on wearing long pants, long sleeved shirt and gloves while mixing/loading.

These MOE values for systemic toxicity were considered acceptable for all scenarios.

3.5.2 Bystanders

For the proposed agricultural use scenarios, bystander exposure should be minimal.

3.5.3 Workers

Post-application systemic dermal exposure estimates were derived using tier one assessment approaches (EPA Standard Operating Procedure for Residential Risk Assessment, 1997), assuming both multiple applications and environmental dissipation (10% per day) and incorporating a dermal absorption value of 8.8%. Post-application inhalation exposure is expected to be negligible.

For both crops a range of re-entry activities take place at different stages of cultivation. For potatoes, scouting was identified as a frequent activity which involved foliar contact and the transfer coefficient for this activity (1500 cm^2/h) was used in the tier one assessment. For grapes, the highest transfer coefficient (10,000 cm^2/h) was associated with turning and tying table grape vines and trellises when foliage development was high, and the re-entry exposure assessment was therefore based on this activity. Based on the nature of the re-entry activities, and the proposed application regime, re-entry exposure would be intermittent over a short to intermediate time frame.

For potato scouts, the maximum estimated exposure (10.7 μg/kg bw/d) occurred after six applications of either Zoxium® 80W Fungicide or Gavel® 75DF Fungicide at 187 g-a.i./ha, at 7-day intervals. For grape re-entry workers, the maximum estimated exposure after eight applications of Zoxium® 80W Fungicide at 224 g-a.i./ha, at 10-day intervals was 69.2 μg/kg bw/d. The maximum exposure resulting from six applications of Gavel® 75DF Fungicide at 187 g-a.i./ha, at 7-day intervals was 71.2 μg/kg bw/d. These exposure estimates are considered conservative as maximum application rates, minimum application intervals, and maximum number of applications proposed on the draft labels were assumed.

MOE values based on systemic dermal exposure and the NOAEL of 62 mg/kg bw/d from the 90-day dog toxicity study are shown below.

Exposure scenario	Zoxium® 80W Fungicide		Gavel® 75DF Fungicide	
	Daily exposure[a] μg/kg bw/d	MOE	Daily exposure[a] μg/kg bw/d	MOE
Potato scout	10.7	5794	10.7	5794
Grape re-entry worker	69.2	896	71.2	871

[a] Absorbed dermal + inhalation dose (assuming dermal absorption = 8.8% and inhalation absorption is equal to absorption through the gastrointestinal tract). Based on wearing long pants, long sleeved shirt and gloves while mixing/loading.

These MOE values for systemic toxicity were considered acceptable.

4.0 Residues

See Appendix III for summary tables.

4.1 Residue summary

Plant (grape and potato) and animal (goat) metabolism studies were conducted using Zoxamide uniformly labelled in the phenyl ring. In grapes, the major residue was observed as parent. Levels of parent were observed at ~0.4 ppm when grapes were treated at 3× good agricultural practice (GAP). The minor cleavage products observed in this study resulted from the cleavage of the peptidic bond and subsequent oxidation. In contrast, no parent was identified in potato tuber. The total radioactive residue (TRR) consisted of two cleavage products, RH-1452 and RH-1455, that were formed when the peptidic bond of the parent molecule was cleaved. The levels of these two metabolites were in the order of 0.04-0.07 ppm when potato plants were treated at 1.5× GAP. In goats, the majority (77% of the TRR) of the uniformly labelled Zoxamide was excreted in the urine and feces. Tissue accumulation was primarily in the excretory organs (0.36 - 0.45 ppm). The maximum observed levels of radiolabeled material in milk occurred at 4 days dosing. The metabolic pathway of Zoxamide in lactating goat was complex. The metabolism of Zoxamide occurred via multiple pathways including hydrolysis, the GSH pathway, reductive dehalogenation, oxidation and conjugation with amino acids and

glucoronic acid. Based on the plant metabolism studies, the ROC in plants is defined as parent in grapes and grape processed fractions and the sum of parent and the two metabolites (RH-1452 and RH-1455) in potato and potato processed fractions.

The residues of Zoxamide per se in or on grape raw agricultrual commodity (RAC), grape processed commodities, potato tubers and wet potato peels were quantified by GC-ECD. A GC-MSD method confirmed the identity of the ROC. For metabolites RH-1452 and RH-1455, in or on potato tubers and potato processed fractions, the GC-MSD method is proposed as the primary method and the GC-ECD method as the confirmatory method. The reported limit of detection (LOD) and the validated LOQ for the analysis of Zoxamide residues in or on grape commodities were 0.003 and 0.01 ppm, respectively. The estimated LOD and validated LOQ, for the analysis of residues of Zoxamide and its acid metabolites in or on potato commodities, were 0.006 and 0.02 ppm, respectively. Each method may be used as the confirmatory method for the other. Both methods were successfully radiovalidated using samples from the grape and potato metabolism studies. These methods were also successfully validated by an independent laboratory. The specificity and resolution of the methods for the quantitation of residues of Zoxamide and its acid metabolites was not examined using other pesticide compounds registered for use on grapes and potatoes. Since a specific method (GC-MSD, monitoring three ions for each analyte) is available, it is unlikely that interferences will be observed.

Geographic representation of grape residue data was completely met with respect to the number and locations of field trials. A total of 12 field trials were conducted over three growing seasons in major grape-growing regions using two formulation classes (WP and DF). These formulations were foliarly applied 10 times to mature and established grape plants at each trial site. Seven trials were conducted using total application rates of 1.4 and 2.8 kg a.i./ha (1.6× the maximum proposed seasonal rate). Five trials were conducted using total rates of 2.24 and 4.48 kg a.i./ha (~1.25× and 2.5×). The petitioner has provided adequate residue data reflecting the maximum proposed use pattern for Zoxamide on grapes. The maximum residues of Zoxamide in or on grapes harvested at the proposed pre-harvest interval (PHI) of 14 days were: (i) 1.18 and 1.49 ppm from samples treated with WP and DF formulations, respectively, at 2.24 kg a.i./ha (1.25×); (ii) 4.53 ppm from samples treated with WP formulation at 2.8 kg a.i./ha(1.6×); (iii) 1.68 ppm from samples treated with WP formulation at 1.4 kg a.i./ha (0.8×); (iv) 4.51 ppm from samples treated with WP formulation at 4.48 kg a.i./ha (2.5×); and (v) 1.74 ppm from samples treated with WP formulation at 1.8 kg a.i./ha (1.0×). A maximum residue limit (MRL) of 3 ppm will be recommended to cover potential residues in grapes.

Twelve field trials were conducted in Canada's major potato-growing zones using two formulation classes (WP and DF). The geographical distribution of these Canadian trials as well as those carried out in the U.S. fulfill the trial zone requirements as specified in the Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*. Both formulations were foliarly applied 10 times, with retreatment intervals of 7 ± 2 days, to mature and established potato plants at 0.2 kg a.i./ha (0.18 lbs a.i./acre/application) for a total seasonal rate of 2.0 kg a.i./ha (1.8 lbs a.i./acre) (1.7× the maximum seasonal rate of

1.12 kg a.i./ha). No residues of Zoxamide and its acid metabolites (RH-1452 and RH-1455) were found above the LOQ (<0.02 ppm) in or on any treated potato samples collected at the proposed 3-day PHI. In addition, a total of 16 field trials were conducted over two growing seasons in major potato-growing regions of the U.S. using two formulation classes (WP and DF). These formulations were foliarly applied 10 times to mature and established potato plants at each trial site. Five trials were conducted using total application rates of 1.4 - 2.8 kg a.i./ha (~1.1× and 2.0× the maximum proposed seasonal rate). Eleven trials were conducted using total rates of 2.2 and 4.4 kg a.i./ha (~2.0× and 4×). At the proposed PHI of 3 days, most treated samples of potatoes bore nondetectable residues of Zoxamide and its acid metabolites RH-1452 and RH-1455, and only a few samples had residues greater than the LOQ (0.02 ppm). Residues quantitated between the estimated LOD and LOQ were presented, but are reported to have a 30% variability. The maximum total residues of Zoxamide and its acid metabolites found in or on potatoes harvested at the proposed 3-day PHI following treatments at ~1.1 - 4.4× were <0.0442 ppm. These data support the establishment of an MRL for the combined residues of Zoxamide and its acid metabolites (RH-1452 and RH-1455, calculated as parent) in or on potato, tuber at 0.06 ppm. An MRL of 0.06 ppm will be proposed to cover these residues in potatoes.

Residues of Zoxamide per se did not concentrate in juice (clarified and unclarified) processed from whole fresh grapes bearing detectable residues. Residues of Zoxamide in grape juice or wine will therefore be covered by the MRL on the RAC. Residues of Zoxamide in raisins concentrated by factors of 5.71×. These concentration factors are corrected for degradation of residues in raisins prior to analysis. The maximum theoretical concentration factor for the processing of grapes to raisins is 4.7× (DIR98-02). Given the uncertainties regarding the freezer storage stability of Zoxamide in raisins, the PMRA has opted to use the theoretical concentration factor (instead of the concentration factor derived from experimental data) to recommend an MRL on raisins. Thus, the proposed MRL level of 15.0 ppm for residues of Zoxamide in or on raisins is recommended.

A potato processing study was submitted. Combined residues of Zoxamide and its acid metabolites (RH-1452 and RH-1455) were 0.047 ppm in/on mature potato tubers following multiple foliar applications of the WP formulation at an exaggerated rate (6.25× the maximum proposed seasonal rate). Residues of Zoxamide and its acid metabolites concentrated 1.20× in chips and 3.98× in flakes. A separate MRL of 0.3 ppm for residues of Zoxamide and its two acid metabolites in potato granules or flakes is recommended to cover residues in domestic and imported potatoes.

For the chronic dietary risk assessment, the potential daily intake (PDI) was determined using the MRLs in or on grapes, potatoes as well as the specific MRL's recommended for processed fractions and the Dietary Exposure Evaluation Model™ (DEEM™) Software. The assessment was conducted using the 1994-1998 Continuing Survey of Food Intake for Individuals. The PDI, including a 10% water allocation, was less than 12% of the acceptable daily intake (ADI = 0.48 mg/kg bw) for the total population, including infants and children. Consequently, the proposed domestic use of Zoxamide on grapes and

potatoes does not pose an unacceptable dietary (both food and water) risk to any segment of the population including infants, children and adults.

5.0 Fate and behaviour in the environment

See Appendix IV for summary tables.

5.1 Physical and chemical properties relevant to the environment

Zoxamide was determined to be sparingly soluble in water, which indicates low potential for the compound to leach in soil or to run off in surface water. The vapour pressure of Zoxamide at 20°C indicates that the compound would be considered relatively non-volatile under field conditions. The Henry's Law constant of Zoxamide indicates that the chemical will be of intermediate volatility from water and moist soil surfaces. The magnitude of the n-octanol-water partition coefficient for Zoxamide indicates a low potential for bioaccumulation. The dissociation constant, pK_a, of the compound could not be measured. The UV-visible absorption spectrum of Zoxamide indicates that the compound was not likely to phototransform at environmentally relevant wavelengths of light.

5.2 Abiotic transformation

Zoxamide hydrolyzed with half-life values of 15.5, 15.7 and 8.1 days at pH 4, 7, and 9, respectively, and the formation of four major transformation products: RH-150721, RH-24549, RH-141288 and RH-129151. These results indicated that Zoxamide was susceptible to hydrolysis at a wide range of pH values, but was rapidly hydrolyzed at alkaline pH. The results of phototransformation studies on soil and in aqueous solution yielded half lives of ~ 7 days and ~ 8 days, respectively. Two major transformation products (RH-24549 and RH-127450) were formed on soil and three major transformation products (RH-150721, RH-24549 and RH-139432) were formed in water.

5.3 Biotransformation

Results of biotransformation studies in soil under aerobic conditions at 20 - 30°C yielded half-life values of 7 - 14 days, with the formation of several minor transformation products. Under anaerobic conditions at 20 - 30°C, the half life in soil was determined to be ~ 15 days, with the formation of two major transformation products, RH-24549 and RH-127450. Results of biotransformation studies in aerobic sediment and water from a river and pond system at 10 - 20°C yielded half-life values of 6 - 21 days, with the formation of two major transformation products, RH-127450 and RH-163353.

5.4 Mobility

The adsorption K_d and K_{oc} values for Zoxamide in five U.S. soils ranged from 3.4 to 25.3 and from 815 to 1431, respectively. The desorption K_d and K_{oc} values ranged from 4.2 to 29.6 and from 927 to 1671, respectively. These results indicate that Zoxamide will be of

low mobility in soil. Based on the values for vapour pressure and Henry's Law constant, volatilization of Zoxamide is not expected to be a route of dissipation.

5.5 Dissipation and accumulation under field conditions

Results of terrestrial field studies of dissipation and accumulation conducted in Canada indicated that Zoxamide was non-persistent in soil, with DT_{50} values ranging from 4.6 to 15 days. No carryover of residues to the next field season is expected to occur based on these results. The transformation products of Zoxamide, however, were not characterized. There was no evidence of leaching of Zoxamide though the soil layers. Field dissipation studies conducted in the U.S. (California and New York) yielded DT_{50} values of 5.8 and 8.2 days, respectively. Zoxamide was detected in the top (0-15 cm) layer of soil. Transformation products were not characterized. The Canadian and U.S. studies are classified as supplementary, owing to deficiencies. Results from the storage stability studies did not provide sufficient information on the storage stability of Zoxamide and transformation products in soil.

5.6 Bioaccumulation

Although the magnitude of the n-octanol-water partition coefficient for Zoxamide ($\log K_{ow} = 3.76$) indicates a potential for bioaccumulation, the results of a bioaccumulation study with bluegill sunfish indicated that Zoxamide has a very low potential to bioaccumulate in organisms.

5.7 Summary of fate and behaviour in the terrestrial environment

Zoxamide was determined to be sparingly soluble in water, which indicates low potential for the compound to leach in soil or to run off in surface water. The vapour pressure of Zoxamide at 20°C indicates that the compound would be considered relatively non-volatile under field conditions. The Henry's Law constant of Zoxamide indicates that the chemical will be of intermediate volatility from water and moist soil surfaces. The magnitude of the n-octanol-water partition coefficient for Zoxamide indicates a low potential for bioaccumulation. The dissociation constant, pK_a, of the compound could not be measured. The UV-visible absorption spectrum of Zoxamide indicates that the compound is not likely to phototransform at environmentally relevant wavelengths of light.

The hydrolytic half-life of Zoxamide was 15.5, 15.7 and 8.1 days at pH 4, 7 and 9, respectively, with the formation of four major transformation products: RH-150721, RH-24549, RH-141288 and RH-129151. Hydrolysis, therefore, will be an important route of transformation of Zoxamide in the terrestrial environment. Zoxamide did not phototransform appreciably on soil. Phototransformation, therefore, will not be a route for transformation or dissipation of Zoxamide on soil.

The half-life of ^{14}C-Zoxamide in loamy sand and silt loam soils under aerobic conditions was 14 days, for both soils, with the formation of several minor transformation products.

The half-life of ^{14}C-Zoxamide in a sandy loam soil under anaerobic conditions was ~14 days, with the formation of two major transformation products, RH-24549 and RH-127450, and several minor transformation products. Based on these results, Zoxamide is classed as non-persistent in soils under aerobic and anaerobic conditions.

The adsorption K_d and K_{oc} values of Zoxamide in five soils (loam, sandy loam, silty clay loam, sandy loam and silty loam) from the U.S. ranged from 3.4 to 25.3 and 815 to 1431, respectively. The desorption K_d and K_{oc} values were similar to those obtained for adsorption. The adsorption data indicated that Zoxamide has a low potential for mobility. The desorption K_{oc} values were higher than the adsorption K_{oc} values, however, indicating that once adsorbed to soil, Zoxamide would be less likely to be mobile in the soil.

Results of terrestrial field studies of dissipation and accumulation conducted in Canada indicated that Zoxamide will be non-persistent in soil and no carryover of the compound to the next field season was expected to occur. These results also indicated that Zoxamide will not leach to lower soil layers. Similar findings were reported from studies conducted in the states of California and New York. The Canadian and U.S. field studies, however, did not satisfy the guideline requirement for terrestrial field studies of dissipation and accumulation because the fate of transformation products was not described or determined and because there were insufficient data on the stability of RH-7281 during storage. Therefore, these studies were classified as supplementary information. Furthermore, results from two storage stability studies did not provide adequate information on the storage stability of Zoxamide and its transformation products in soil.

Although the magnitude of the n-octanol-water partition coefficient for Zoxamide ($\log K_{ow} = 3.76$) indicates a potential for bioaccumulation, the results of a bioaccumulation study with bluegill sunfish indicated that Zoxamide has a very low potential to bioaccumulate in organisms.

5.8 Summary of fate and behaviour in the aquatic environment

The hydrolytic half-life of Zoxamide was 15.5, 15.7 and 8.1 days at pH 4, 7 and 9, respectively, with the formation of four major transformation products: RH-150721, RH-24549, RH-141288 and RH-129151. Hydrolysis, therefore, will be an important route of transformation of Zoxamide in the aquatic environment. Zoxamide photolysed in aqueous solution with a half-life of ~15 days. Phototransformation, therefore, may be a route of transformation in the photic zone of clear natural water.

The half-life of ^{14}C-Zoxamide in two aerobic sediment and water systems at 10 - 20°C ranged from 6 to 21 days, with the formation of two major transformation products: RH-127450 and RH-163353. Based on these results, Zoxamide is classed as non-persistent to slightly persistent in aerobic sediment and water.

Results of a bioaccumulation study with bluegill sunfish, *Lepomis macrochirus*, indicated that Zoxamide was both rapidly absorbed and rapidly excreted by the sunfish. These results indicate that Zoxamide has a low potential to bioaccumulate in fish.

5.9 Expected environmental concentrations

The concentrations of Zoxamide in various environmental compartments were estimated based on calculations using maximum-exposure scenarios. It was asssumed that, per the Canadian label for Zoxium® 80W Fungicide, a maximum of 8 applications per growing season were made at intervals of 7 days, at the maximum label rate of 0.224 kg a.i./ha. A half-life of 15 days on soil and 21 days in water was used in these calculations. The resulting value is referred to as the "maximum label rate".

5.9.1 Soil

Assuming a soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm and a scenario in which the "maximum label rate" is applied to bare soil, the expected environmental concentration (EEC) of residues in soil would be 0.33 mg a.i./kg soil.

5.9.2 Aquatic systems

Assuming a water density of 1.0 g/mL, a water depth of 30 cm and a scenario in which a body of water is over-sprayed with the "maximum label rate," the EEC in water would be 0.31 mg a.i./L water.

5.9.3 Vegetation and other food sources

The applicant did not submit data on the concentrations of Zoxamide on crops immediately after application. Residue concentrations on vegetation, therefore, were estimated using a nomogram developed by the EPA from the data of Hoerger and Kenaga (1972), for use in ecological risk assessment (Urban and Cook, 1986) (Table 4, Appendix IV). A wet weight to dry weight conversion was also calculated.

6.0 Effects on non-target species

See Appendix IV for summary tables.

6.1 Effects on terrestrial organisms

The 14-day LC_{50} and no observable effect concentration (NOEC) for the earthworm, *Eisenia foetida*, were > 1070 mg a.i./kg soil and 66.7 mg a.i./kg soil, respectively. The acute contact LD_{50} of Zoxamide for the honeybee, *Apis mellifera*, was > 100 μg a.i./bee and the acute oral and contact LD_{50} of Mancozeb and Zoxamide blend for the same species was > 200 and > 153 μg/bee. Zoxamide and a blend of Mancozeb and Zoxamide are non-toxic to the honeybee according to the criteria of Atkins *et al.* (1981).

The acute (14-day) oral LD_{50} of Zoxamide for the bobwhite quail (*Colinus virginianus*) was > 2000 mg a.i./kg bw. The acute (8-day) dietary LC_{50} of Zoxamide for the bobwhite quail and the mallard duck (*Anas platyrhynchos*) was > 5250 mg a.i./kg diet, for both species. The NOEC of Zoxamide on the reproduction of the bobwhite and the mallard was 1000 mg a.i./kg diet, for both species. Based on the results of the toxicity studies, Zoxamide is classified as practically non-toxic to bobwhite quail on an acute basis and practically non-toxic to bobwhite quail and mallard duck on a dietary basis, in accordance with the classification system of the EPA.

Zoxamide was determined to be practically non-toxic to rats when administered as a single dose via the oral route (LD_{50} > 5000 mg/kg bw). Zoxamide was reported to be of low toxicity to rats when administered via the dermal route (LD_{50} > 2000 mg/kg bw). Zoxamide was also of low toxicity to rats when administered by the inhalation route (LC_{50} > 5.3 mg/L). Zoxamide was found to be non-irritating to the skin and mildly irritating to the eye of rabbits, and a strong sensitizer to the skin of guinea pigs.

Repeated short-term oral dosing of Zoxamide to Beagle dogs resulted in lower body weight gains, lower food efficiency, lower albumin, increased liver weight accompanied by diffuse hepatocellular hypertrophy, and liver effects (no observable adverse effect level (NOAEL) = 62 mg/kg bw/d for females and 281 mg/kg bw/d for males). Oncogenicity in studies with mice and rats indicated a trend for increase in bronchioalveolar adenoma and increased liver weights in females (NOAEL = 1021 and 1058 mg/kg bw/d, respectively). Zoxamide was not genotoxic and non-mutagenic in a standard battery of genotoxicity and mutagenicity tests. Zoxamide was not neurotoxic to rats and non-teratogenic to rats and rabbits.

In a multi-generation reproduction study with rats (effects on pregnancy and fetuses), Zoxamide caused no adverse effects on the outcome of pregnancy nor the development of the fetuses (NOAEL = 2091 mg/kg bw/d, for reproductive effects).

Although not verified owing to inadequate reporting of raw data, the results of a multi-dose phytotoxicity study conducted with Zoxamide indicated that pre- or post-emergent applications of up to 500 g a.i./h did not cause chlorosis, necrosis, malformations or growth inhibition in 17 crop species tested: corn, cotton, wheat, rice, barley, cabbage, carrots, lettuce, melon, onion, peas, rape, rye, sugar beets, sunflower, tomato, and soybean. Similar results were obtained for formulated Zoxamide, applied at a rate of up to 500 g a.i./h, for eight broadleaf weed species, eight grassy weed species, and five crop species: corn, cotton, wheat, rice and soybean.

6.2 Effects on aquatic organisms

The acute (48-h) EC_{50} of Zoxamide to the water flea, *Daphnia magna*, was > 0.78 mg a.i./L and the chronic (21-day) EC_{50} of Zoxamide to the same species was 0.085 mg a.i./L (~ 85 μg a.i./L). The acute (48-h) EC_{50} of Mancozeb and Zoxamide blend to *D. magna* was 3.8 mg/L. The chronic NOEC of Zoxamide to *D. magna* and the midge, *Chironomus riparius*, were 0.039 mg a.i./L (~ 39 μg a.i./L) and 0.21 mg a.i./L (~ 210 μg a.i./L),

respectively. Based on the results of these studies, Zoxamide is classified as highly toxic on an acute basis and very highly toxic on a chronic basis to *D. magna* in accordance with the classification system of the EPA. The blend of Mancozeb and Zoxamide is classified as moderately toxic to daphnids in accordance with the classification system of the EPA.

The acute (96-h) LC_{50} of Zoxamide to the saltwater mysid, *Mysidopsis bahia*, and the acute (96-h) EC_{50} (for shell deposition) to the eastern oyster, *Crassostrea virginica*, were 75 μg a.i./L and 715 μg a.i./L, respectively. The chronic (27-day) NOEC to *M. bahia* was 7.2 μg a.i./L. Based on the results of the toxicity studies, Zoxamide is classified as very highly toxic to *M. bahia* and highly toxic to *C. virginica* on an acute basis in accordance with the classification system of the EPA.

The acute (96-h) LC_{50} of Zoxamide to the rainbow trout (*Oncorhynchus mykiss*), the bluegill sunfish (*Lepomis macrochirus*) and the sheepshead minnow (*Cyprinodon variegatus*) were 156 μg a.i./L, > 790 μg a.i./L and > 860 μg a.i./L, respectively. The acute (96-h) LC_{50} of the Mancozeb and Zoxamide blend to *O. mykiss* was 1.9 mg/L. The NOEC of Zoxamide for the early life-stages of the rainbow trout and the sheepshead minnow were 3.48 μg a.i./L and 40 μg a.i./L, respectively, and for a full life cycle in the fathead minnow (*Pimephales promelas*) 60 μg a.i./L. Based on the results of the toxicity studies, Zoxamide is classified as highly toxic to the rainbow trout, the bluegill sunfish and the sheepshead minnow on an acute basis in accordance with the classification system of the EPA. The blend of Mancozeb and Zoxamide is classified as moderately toxic to the trout on an acute basis in accordance with the classification system of the EPA.

The acute EC_{50} of Zoxamide to the algae, *Selenastrum capricornutum*, *Anabaena flos-aquae* and *Scenedesmus subspicatus*; the freshwater diatom, *Navicula pelliculosa*; and the marine diatom, *Skeletonema costatum*, were 23 μg a.i./L, 860 μg a.i./L and 10 μg a.i./L, respectively. The chronic 14-d EC_{50} of Zoxamide to the alga, *S. capricornutum* was 19 μg a.i./L. The acute EC_{50} of the Mancozeb and Zoxamide blend to *S. capricornutum* was 29.5 μg a.i./L.

6.3 Effects on biological methods of sewage treatment

Not applicable for the proposed use.

6.4 Risk characterization

6.4.1 Environmental behaviour

Zoxamide is slightly persistent in water. It is not expected to volatilize from water and moist soils. The principal routes of transformation are biotransformation in soil and in aquatic environments. The persistence and mobility of the major transformation products RH-24549, RH-141288, RH-127450, and RH-139432 are unknown.

6.4.2 Terrestrial organisms

The risk to non-target organisms was calculated using EEC values of 0.33 mg a.i./kg in soil 15-cm deep and 0.31 mg a.i./L in water 30-cm deep water. The EEC values in wildlife food sources, expressed in mg a.i./kg dw, are shown in Table 4, Appendix IV. Margins of safety (MOS) were calculated using the NOEC, an estimated NOEC equivalent to 1/10 of the EC_{50} or LC_{50}, or an estimated NOEC equivalent to 1/10 of the EC_{50} or LC_{50} for the most sensitive species per group.

Non-target terrestrial invertebrates
The acute NOEC of Zoxamide to the earthworm, *Eisenia foetida*, is < 66.7 mg a.i./kg soil. Given that the maximum residue of Zoxamide in soil EEC in soil would be 0.33 mg a.i./kg soil, Zoxamide will not pose a risk (MOS = >200) to terrestrial invertebrates such as the earthworm.

The acute contact LD_{50} of Zoxamide to the honeybee, *Apis mellifera*, is > 100 μg a.i./bee. Based on Atkins *et al.* (1981), this value is equivalent to 112 kg a.i./ha. Given that the maximum residue of Zoxamide on vegetation EEC on leafy crops will be 924 mg a.i./kg, Zoxamide will not pose a risk (MOS = > 20000) to terrestrial invertebrates, such as the honeybee.

Terrestrial plants
The results of a multi-dose phytotoxicity study conducted with Zoxamide indicated that, pre- or post-emergent applications of up to 500 g a.i./h did not cause chlorosis, necrosis, malformations or growth inhibition in 17 crop species tested: corn, cotton, wheat, rice, barley, cabbage, carrots, lettuce, melon, onion, peas, rape, rye, sugar beets, sunflower, tomato, and soybean.

These results indicate that Zoxamide will not pose an appreciable risk to non-target vegetation if exposure of the non-target vegetation occurs by spray drift, assuming that only up to 10 % of the applied material is transported to vegetation by spray drift.

Wild birds
The most sensitive end point is adverse effects on reproduction of the bobwhite quail, *Colinus virginianus*, and the mallard duck, *Anas platyrhynchos*, with a NOEC of 1000 mg a.i./kg diet for both species.

Wild birds, such as bobwhite quail and mallard duck, could be exposed to Zoxamide residues as a result of spray drift or consumption of sprayed vegetation or contaminated prey.

The bobwhite diet may consist of approximately 27 % small insects and 73 % seeds (EPA, 1993). Since the EEC values of Zoxamide on small insects and pods with seeds are 148.2 and 31.3 mg a.i./kg dry weight, respectively (Table 4, Appendix IV), the estimated ingestion of Zoxamide via contaminated food sources by the bobwhite can be calculated as follows:

$(0.27 \times 148.2) + (0.73 \times 31.3) = 62.8$ mg a.i./kg dry weight

The bobwhite quail (live weight = 170 g) daily consumes food equivalent to 8.94 % of its body weight (Urban and Cook, 1986). Therefore, the bird would acquire a dose of:

$(0.089 \times 170) \times 62.8 \div 1000 = 0.95$ mg a.i./d
equivalent to: $(1000 \div 170) \times 0.95 =$ **5.58** mg a.i./kg bw/d

The mallard duck diet may consist of approximately 10 % large insects or snails, 10 % leafy plants and 80 % grain (EPA, 1993). Since the EEC values of Zoxamide on large insects, leaves and leafy plants and grain, are 25.36, 924.0 and 25.36 mg a.i./kg dry weight, respectively (Table 4, Appendix IV), the estimated ingestion of Zoxamide through contaminated food sources by the mallard can be calculated as follows:

$(0.10 \times 25.36) + (0.10 \times 924.0) + (0.80 \times 25.36) = 115.2$ mg a.i./kg dry weight

The mallard duck (live weight = 1.2 kg) daily consumes food equivalent to 4.17 % of its body weight (Urban and Cook, 1986). Therefore, the bird would acquire a dose of:

$(0.041 \times 1200) \times 115.2 \div 1000 = 5.66$ mg a.i./d
equivalent to: $(1000 \div 1200) \times 5.66 =$ **4.71** mg a.i./kg bw/d

These values are lower than the NOEC values for the bobwhite quail and the mallard duck (converted to mg a.i./kg bw/d) at which there were no adverse reproductive effects on the test birds. It is, therefore, expected that Zoxamide will not pose a risk to the bobwhite quail (MOS = 16) or the mallard duck (MOS = 9) on a reproductive effects basis.

Wild mammals

The most likely route for exposure of wild mammals to Zoxamide would be through consumption of contaminated prey or vegetation following operational applications of Zoxium® 80W fungicide. Assuming a maximum residue of 530.0 mg a.i./kg in short range grass (dry weight basis), and 148.2 mg a.i./kg in small insects (dry weight basis), dosage levels immediately following application resulting from several maximum-exposure scenarios can be estimated. For example, the eastern cottontail rabbit (live weight = 1.3 kg), *Sylvilagus floridanus*, consuming short grass at a rate of 4.4 % of its body weight per day (Dalke and Sime, 1941; Banfield, 1974), would consume 57.2 g of food per day and acquire a dose of 23.3 mg a.i./kg bw/d. The masked shrew (live weight = 4 g), *Sorex cinereus*, ingesting 25-75 % of its body weight per day of contaminated small insects (Banfield, 1974) would consume 1 to 3 g of food per day and acquire a dose of 37.05 to 111.15 mg a.i./kg bw/d. The meadow vole (live weight = 3.5 g), *Microtus pennsylvanicus*, ingesting 15-24 % of its body weight per day in grasses (Peterson, 1966) would consume 0.52 to 0.84 g of food per day and acquire a dose of 78.7 to 127.2 mg a.i./kg bw/d.

These estimated exposure dosages are less than the LD_{50} from any of the acute toxicity studies, but exceed the NOEL values from some of the sub-chronic and chronic studies. The results from some of these latter studies, however, likely overstate the effects that may occur in the field. The proposed use of Zoxium® 80W fungicide in the field will result in limited exposure of Zoxamide to wild mammals and, therefore, is not expected to pose an appreciable risk to wild mammals.

6.4.3 Aquatic organisms

Non-target aquatic invertebrates
The most sensitive end point is chronic effects on the water flea, *Daphnia magna*, with an EC_{50} of 39 μg a.i./L. Given that the EEC of Zoxamide in water will be 310 μg a.i./L, Zoxamide will pose a moderate risk (MOS = 0.12) to aquatic invertebrates, such as the water flea.

Non-target marine and estuarine invertebrates
The most sensitive end point is chronic effects on the saltwater mysid, *Mysidopsis bahia*, with a NOEC of 7.2 μg a.i./L. Given that the EEC of Zoxamide in water will be 310 μg a.i./L, Zoxamide will pose a high risk (MOS = 0.02) to marine and estuarine invertebrates, such as the saltwater mysid.

Fish
The most sensitive end point is adverse effects on early life-stages of the rainbow trout, *Oncorhynchus mykiss*, with a NOEC of 3.48 μg a.i./L. Given that the EEC of Zoxamide in water will be 310 μg a.i./L, Zoxamide will pose a high risk (MOS = 0.01) to fish.

Aquatic plants and algae
The most sensitive end point is adverse effects on the freshwater alga, *Selenastrum capricornutum*, with an acute NOEC of 4.1 μg a.i./L. Given that the EEC of Zoxamide in water will be 310 μg a.i./L, Zoxamide will pose a high risk (MOS = 0.01) to aquatic organisms, such as the freshwater alga.

6.5 Risk mitigation

The environmental fate and toxicity of the following major transformation products of Zoxamide under field conditions are unknown: RH-24549, RH-141288, RH-127450, and RH-139432. There are inadequate data on the toxicity of Zoxamide to terrestrial plants. Zoxamide will pose a high risk to aquatic invertebrates, such as the water flea, and a very high risk to fish, marine and estuarine invertebrates, and aquatic plants and algae.

The risk to terrestrial plants and aquatic organisms can be mitigated by the establishment of terrestrial and aquatic buffer zones.

Mitigative measures
A buffer zone of **25 m** for application by ground boom sprayer, and a buffer zone of **35 m** for application by air-blast or vineyard sprayer, should be established between the last spray swath and the edge of aquatic systems such as rivers, lakes, ponds, streams and other bodies of water.

A buffer zone of **5 m** for application by ground boom sprayer, and a buffer zone of **10 m** for application by air-blast/vineyard sprayer, should be established between the last spray swath and the edge of terrestrial habitats such as hedgerows, windbreaks, woodlots, vegetative strips and other vegetation.

Aerial application
Aerial drift is increased under certain meteorological conditions. Do not apply during periods of dead calm, when winds are gusty or when wind speed is greater than 15 km/h at flying height at the site of application. Do not use a boom height greater than 3 m above canopy.

For the protection of non-target habitats, overspray or drift to sensitive habitats must be avoided. A **buffer zone of 20 m** is required between the downwind edge of the boom and the closest edge of sensitive aquatic habitats such as lakes, rivers, streams, sloughs, ponds, creeks and reservoirs. Do not contaminate these habitats when cleaning and rinsing spray equipment or containers.

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended use

Rohm and Haas Canada has applied for the registration of two commercial class end use products with the trade names Gavel® 75DF Fungicide and Zoxium® 80W Fungicide. These products are different formulations containing the new fungicide active ingredient Zoxamide. The following uses were proposed for registration:

Gavel® 75DF Fungicide on potatoes
For control of late blight, early blight and tuber rot apply Gavel® 75DF Fungicide every 5 - 7 days when late blight is present and environmental conditions favour continued disease development. Under low disease pressure and environmental conditions unfavourable for disease development, apply every 7 - 10 days. Apply 1.7 kg/ha (1.134 Mancozeb + 0.141 Zoxamide kg a.i./ha) when plants are 10 to 15 cm high. Increase the rate at 2.0 kg/ha (1.334 Mancozeb + 0.166 Zoxamide kg a.i./ha) as plants increase in size and to 2.25 kg/ha (1.5 Mancozeb + 0.187 Zoxamide kg a.i./ha) at row closure. Maximum of 10 applications per season with a 3 day PHI.

Gavel® 75DF Fungicide on grapes
For the control of downy mildew and black rot apply Gavel® 75DF Fungicide at 2.25 - 2.8 kg product/ha starting when new shoots are 1 - 4 cm long, repeat at 8 - 12 cm and at 20 - 25 cm. Continue applications on a 7- to 10-day interval when conditions are favourable to disease development.

Maximum of six applications per season with a 30-day PHI.

Zoxium® 80W Fungicide on potatoes
Apply 140 g a.i./ha when plants are 10 - 15 cm high, 180 g a.i./ha as plant increase in size and 224 g a.i./ha at row closure for control of late blight and tuber rot caused by *Phytophthora infestans* on potatoes. Apply on a 5- to 7-day schedule with a maximum of 10 applications per season.

For additional control of early blight caused by *Alternaria solani* tankmix Zoxium® 80W Fungicide with Dithane® DG Rainshield NT Fungicide (Mancozeb) at a rate of 1.125 - 1.5 kg a.i./ha on a 5- to 10-day interval.

Zoxium® 80W Fungicide on grapes
For control of downy mildew, apply 140 - 224 g a.i./ha increasing the rate with vine growth. Begin applications when the new shoots are 1 - 4 cm long and repeat when shoots are 8 - 12 cm long and again when 20 - 25 cm long. Continue applications on a 7- to 10-day interval when conditions are favourable for disease development. Do not apply more than eight applications per season with a PHI of 14 days.

For control of powdery mildew and black rot tankmix Zoxium® 80W Fungicide with Nova® 40W Fungicide (Myclobutanil) at 80 g a.i./ha on a 14- to 21-day interval.

7.1.2 Mode of action

Zoxamide causes the disruption of the microtubule cytoskeleton and arrest nuclear division by binding specifically to tubulin. When 14C- Zoxamide was applied to intact Phytophthora capsici cells followed by separation of the radiolabeled protein and autoradiography, it was found to bind covalently to only one protein in the cell, the β-subunit of tubulin. A plant mobility study with radiolabeled product shows that there is very little movement of Zoxamide out of the treated area on the plant.

7.1.3 Effectiveness against pest

7.1.3.1 Gavel® 75DF Fungicide

Potatoes

Late blight (*Phytophthora infestans*)
Sixteen trials were reviewed, and in all trials the Zoxamide + Mancozeb treatments were significantly different from the check. In 15 trials, Zoxamide + Mancozeb provided the same or higher level of disease control than the commercial standard, Mancozeb.

The data did not support the use of different rates according to the crop growth stage. The trials consistently demonstrate a differential response between high and low rate in response to disease pressure. When environmental conditions favour late blight development, the high rate provides significantly higher disease control than the low rate. Two trials demonstrated that the proposed rates failed to provide adequate disease control when the spraying interval is extended beyond 7 days.

Only one trial provided information on aerial application. The results demonstrated that Gavel® 75DF Fungicide applied in 45 - 90 L water/ha provided disease control comparable to a registered alternative.

Review of the efficacy data supports the late blight control claims as follow:

"For control of late blight under high disease pressure apply Gavel® 75DF Fungicide 2.25 kg/ha (1.5 Mancozeb + 0.187 Zoxamide kg a.i./ha) every 7 days when late blight is present and environmental conditions favour continued disease development. Under low disease pressure or environmental conditions unfavourable for disease development apply Gavel® 75DF Fungicide every 7 days at 1.7 kg/ha (1.134 Mancozeb + 0.141 Zoxamide kg a.i./ha). Maximum of 6 applications per season with a 3 day PHI. For aerial spray, apply in 45 - 90 L water/ha. Use 90 L water/ha under high disease pressure."

Tuber rot (*Phytophthora infestans*)
Eleven trials conducted over four years were reviewed. The weight of evidence indicates that the decreased tuber rot incidence following Zoxamide applications was due to a decrease in sporulation at harvest time resulting from season long foliar late blight control. Season-long applications of Zoxamide and registered fungicides do not protect the tubers from infection during harvest. Further information will be needed to prove conclusively that Zoxamide can reduce tuber rot by decreasing the vitality of late blight zoospores *in vivo*. The tuber rot control claim independent of foliar late blight control is not acceptable for registration.

Early blight (*Alternaria solani*)
Eight trials were reviewed; two of those trials could not be used because the disease incidence was too low.

The data on early blight control demonstrated that Zoxamide alone has minimal effect on this disease. The disease control effect is due to the Mancozeb component of this product which is already registered for this use. In all trials, Zoxamide with Mancozeb provided higher or similar level of disease control than Mancozeb applied at registered rates.

Review of the efficacy data supports the late blight and early blight control claims as follow:

"For control of late blight and early blight apply Gavel® 75DF Fungicide at 2.25 kg/ha (1.5 Mancozeb + 0.187 Zoxamide kg a.i./ha) every 7 days under high disease pressure when either disease is present and environmental conditions favour continued disease development. Under low disease pressure and environmental conditions unfavourable for disease development apply Gavel® 75DF Fungicide every 7 days at 1.7 kg/ha (1.134 Mancozeb + 0.141 Zoxamide kg a.i./ha). Maximum of 6 applications per season with a 3 day PHI. For aerial spray, apply in 45 - 90 L water/ha. Use 90 L/ha under high disease pressure."

Chemigation application
Chemigation application of Gavel® 75DF Fungicide on potatoes is not acceptable, since none of the trials submitted used chemigation.

Grapes

Downy mildew (*Plasmopara viticola*)
The three U.S. trials reviewed did not support the proposed claim for downy mildew by themselves. Previously reviewed Zoxium® 80W Fungicide data and the registered uses of Mancozeb for downy mildew control allowed consideration of only the low rate proposed for registration. No trials tested the proposed high rate.

The data indicate that much lower rates could be efficacious for downy mildew control; however, further efficacy trials are required to establish the lowest efficacious rate. The following claim is acceptable:

"Apply Gavel® 75DF Fungicide at 2.25 kg product/ha starting when new shoots are 1 - 4 cm long, repeat at 8 - 12 cm and at 20 - 25 cm. Continue applications on a 7- to 10-day intervals when conditions are favourable to disease development. Maximum of 6 applications per season with a 66-day PHI."

Black Rot (*Guignardia bidwelli*)
The two black rot trials available were not acceptable. Efficacy trials will be required to establish the lowest efficacious rate for black rot control. The proposed black rot control claim is unacceptable.

Chemigation and aerial application:
Aerial and chemigation application of Gavel® 75DF Fungicide on grapes are not acceptable, since all the trials submitted were carried out using ground application.

7.1.3.2 Zoxium® 80W Fungicide

Potatoes

Late blight (*Phytophthora infestans*)
Zoxium® 80W Fungicide applied alone:
Eight trials conducted in Canada and the U.S. over four years were reviewed. Review of the late blight data shows that Zoxamide applied alone does not provide consistent disease control even under low disease pressure. In two out of six trials supporting the proposed claim, the level of disease control provided by Zoxamide was significantly lower than the registered commercial standard under the same conditions.

The proposed claim for foliar late blight control with Zoxamide applied alone is not acceptable.

Zoxium® 80W Fungicide + Dithane® DG Rainshield NT Fungicide (Mancozeb) tankmix:
Tankmixing Zoxamide with Mancozeb provided equal or higher disease control than Mancozeb applied alone at the highest registered rate. The 16 trials that support the use of the formulated mix, Gavel® 75DF Fungicide, were also used to support the use of a tankmix using the same application rates. The claim for aerial application is acceptable at 45 - 90 L/ha using the 90 L/ha rate under high disease pressure based on the data submitted for aerial application of Gavel® 75DF Fungicide. The use of a Zoxamide with Mancozeb tankmix is acceptable as follows:

"Under low disease pressure, tankmix 175 g Zoxium® 80W Fungicide + 1.5 kg Dithane® DG Rainshield NT Fungicide (140 g Zoxamide + 1.13 kg of Mancozeb). Under high disease pressure tankmix 235 g Zoxium® 80W Fungicide + 2.0 kg Dithane® DG Rainshield NT Fungicide (188 g of Zoxamide + 1.5 kg of Mancozeb). Apply at 7-day interval. Maximum of 6 applications per season with a 3-day PHI. For aerial spray, apply in 45 to 90 L water/ha. Use 90 L/ha under high disease pressure."

Tuber rot (*Phytophthora infestans*)
Eleven trials conducted over four years were reviewed. The weight of evidence indicates that the decrease observed in tuber rot control following Zoxamide applications is due to a decrease in sporulation at harvest time resulting from season long foliar late blight control. Season-long applications of Zoxamide and registered fungicides do not provide consistent protection of the tubers from infection during harvest. Further information will be needed to demonstrate conclusively that Zoxamide can reduce tuber rot by decreasing the vitality of late blight zoospores in the field. The tuber rot control claim is not acceptable for registration.

Early blight (*Alternaria solani*)
Eight trials were reviewed and two of those trials could not be used because the disease incidence was too low. The data on early blight control demonstrated that Zoxamide applied alone provided unacceptable control of early blight. The disease control effect is

due to the Mancozeb component of this product which is already registered for this use. In all trials, however, Zoxamide with Mancozeb provided higher or similar level of disease control than Mancozeb applied alone at registered rates.

Review of the efficacy data support the late and early blight control claims for the Zoxamide with Mancozeb tank mix as follows:

"For control of late blight and additional control of early blight apply 175 g Zoxium® 80W Fungicide tankmixed with 1.5 kg Dithane® DG Rainshield NT Fungicide (140 g Zoxamide + 1.13 kg of Mancozeb) under low disease pressure or when environmental conditions are unfavourable for disease development. Under high disease pressure when late blight is present and environmental conditions favour continued disease development apply 235 g Zoxium® 80W Fungicide tankmixed with 2.0 kg Dithane® DG Rainshield NT Fungicide (187 g Zoxamide + 1.5 kg Mancozeb). Use a 7-day interval between each application with a maximum of 6 applications per season and a 3-day PHI. For aerial spray, apply in 45 - 90 L water/ha. Use 90 L/ha under high disease pressure."

Chemigation application
Chemigation application of Zoxium® 80W Fungicide is not acceptable, since none of the trials submitted used chemigation.

Grapes

Downy mildew (*Plasmopara viticola*)
Twelve trials were reviewed. The data shows that the rate of application is not related to the growth stage of vines but to the disease pressure. Under low to moderate disease pressure, season-long disease control was provided by the low rate (140 g a.i./ha) of application. Under high disease pressure, however, the high application rate (224 g a.i./ha) provided significantly higher disease control than the low rate.

Review of the data does not support the proposed application interval of 7- to 10-days, since only one trial used 10 days between application interval, while most others used 14 days. No trials provided information on an interval lower than 10 days.

Based on published strategies for the prevention of disease resistance, alternation with a fungicide having a different mode of action is recommended after two sequential applications instead of after three as proposed on the draft label.

Powdery mildew (*Uncinula necator*) and black rot (*Guignardia bidwellii*)
Seven trials provided information on the effect of tankmixing Zoxamide with Myclobutanil on powdery mildew and black rot. No interactions (precipitation in the tank, phytotoxicity, effect on efficacy) were found between Zoxamide and Myclobutanil when tankmixed. Although one trial showed that Zoxamide could control black rot, there is not enough data to demonstrate consistent black rot control. The only conclusion that can be drawn from these trials is that tankmixing Zoxamide with Myclobutanil does not affect the performance of Myclobutanil to control powdery mildew and black rot. As a

result, the use of tankmixing with Myclobutanil for control of powdery mildew and black rot is acceptable, since Myclobutanil is already registered for control of those two diseases.

Review of the efficacy data supports the claims for downy mildew, powdery mildew and black rot control as follows:

"For control of downy mildew apply 175 to 280 g Zoxium® 80W Fungicide (140 - 224 g a.i./ha) beginning the applications when the new shoots are 1 - 4 cm long and repeat when shoots are 8 - 12 cm long and again when 20 - 25 cm long. Continue applications on a 7- to 10-day interval when conditions are favourable to disease development. Alternate Zoxium® 80W Fungicide with a fungicide having a different mode of action after two sequential applications of Zoxium® 80W Fungicide. Use the high rate and short application interval under heavy disease pressure. Do not make more than 8 applications per season."

Zoxium® 80W Fungicide can be tankmixed with Nova® 40W Fungicide (Myclobutanil) at label rate for control of powdery mildew and black rot. Follow the Nova® 40W Fungicide (Myclobutanil) use directions for rate and timing.

Chemigation and aerial application
Aerial and chemigation application of Zoxium® 80W Fungicide on grapes are not acceptable, since all the trials submitted were carried out using ground application.

7.2 Phytotoxicity to target plants

No phytotoxicity was noted for either formulation.

7.3 Sustainability

7.3.1 Survey of alternatives

See Appendix V, Tables 3 and 4 for a summary.

7.3.2 Compatibility with current management practices including IPM

Integrated pest management (IPM) programs developed for disease control have several features in common. Those include sanitation measures to deal with crop debris, control of alternative hosts, cultural practices to decrease the chance of infection (i.e., hilling of potatoes to keep the tubers well covered with soil and less exposed to infection; thinning and pruning in grapes to improve ventilation and reduce leaf wetness). Equally important is the use of resistant or less susceptible varieties when they are available. Weather and field monitoring to watch for conditions favourable to disease development and to identify when a disease is present or to establish accurately the crop growth stage are essential for optimal application timing. The use of Zoxamide and fungicides in general is compatible with such programs, since they complement each other. The use of an IPM

program, including registered fungicides, like Zoxamide, will result in more effective control of economically important diseases.

7.3.3 Contribution to risk reduction

Zoxamide provides an alternative chemistry and a new mode of action for the control of late blight and downy mildew, which have both developed resistance to some of the fungicides currently registered for their control. In combination with Mancozeb Zoxamide allows the use of reduced application rate of Mancozeb which has been identified for re-evaluation by the PMRA and the EPA.

7.3.4 Information on the occurrence or possible occurrence of the development of resistance

According to DIR99-06, *Voluntary Pesticide Resistance Management Labelling Based on Target Site/Mode of Action*, the following statements will be incorporated in all Zoxamide containing end-use product labels.

Zoxium® 80W Fungicide

GROUP	22	FUNGICIDE

Resistance management recommendations
For resistance management, please note that Zoxium® 80W Fungicide contains a Group 22 fungicide. Any fungal population may contain individuals naturally resistant to Zoxamide. A gradual or total loss of pest control may occur over time if this fungicide is used repeatedly in the same fields. Other resistance mechanisms that are not linked to site of action but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed. To delay fungicide resistance:

- Avoid application of more than two consecutive sprays of Zoxium® 80W Fungicide or other fungicides in the same group in a season.
- Use tank mixtures with fungicide from a different group when such use is permitted.

Gavel® 75DF Fungicide

GROUP	22 M	FUNGICIDE

Resistance management recommendations
For resistance management, please note that Gavel® 75DF Fungicide contains both a Group 22 and Group M fungicide. Any fungal population may contain individuals naturally resistant to Zoxamide and other Group 22 or Group M fungicides. A gradual or total loss of pest control may occur over time if these fungicides are used repeatedly in the same fields.

Resistance management recommendations common to both products

- Fungicide use should be based on an IPM program that includes scouting, historical information related to pesticide use and crop rotation, and considers cultural, biological and other chemical control practices.

- Monitor treated fungal populations for signs of resistance development.

- If the disease continues to progress after treatment with this product, do not increase the use rate. Discontinue use of this product, and switch to another fungicide with a different target site of action, if available.

- Contact your local extension specialist or certified crop advisors for any additional pesticide resistance management and IPM recommendations for specific crops and pathogens.

- For further information and to report suspected resistance, contact Rohm and Haas Company at 1-800-268-4201 or at www.rohmhaas.com.

7.4 Conclusions

Gavel® 75DF Fungicide
Adequate efficacy and value data have been provided to support ground and aerial application of Gavel® 75DF Fungicide to control late and early blight on potatoes at 1.7 - 2.25 kg/ha with a maximum of six applications per seasons. Insufficient data have been provided to support the tuber rot control claim.

Adequate efficacy and value data have been provided to support ground application of Gavel® 75DF Fungicide to control downy mildew on grapes at 2.25 kg/ha with a maximum of six applications per seasons. Insufficient data have been provided to support the black rot control claim.

The data provided indicates that Gavel® 75DF Fungicide can be applied for the control of late and early blight on potatoes and downy mildew on grapes.

Zoxium® 80W Fungicide
Adequate efficacy and value data have been provided to support ground and aerial application of Zoxium® 80W Fungicide tankmixed with Mancozeb, 175 g Zoxium® 80W Fungicide + 1.5 kg Dithane® DG Rainshield NT Fungicide under low disease pressure and 235 g Zoxium® 80W Fungicide + 2.0 kg Dithane® DG Rainshield NT Fungicide

under high disease pressure, to control late and early blight on potatoes with a maximum of six applications per seasons. Insufficient data have been provided to support the tuber rot control claim.

Adequate efficacy and value data have been provided to support ground application of Zoxium® 80W Fungicide to control downy mildew on grapes at 175 - 235 g/ha with a maximum of eight applications per season. The data also support tankmixing with Nova® 40W Fungicide (Myclobutanil) for powdery mildew and black rot control.

The data provided indicates that Zoxium® 80W Fungicide can be applied in a tankmix with Dithane® DG Rainshield NT Fungicide (Mancozeb) for the control of late and early blight on potatoes and alone for control of downy mildew or in a tankmix with Nova® 40W Fungicide (Myclobutanil) for control of powdery mildew and black rot on grapes.

See Appendix V, Tables 1 and 2.

8.0 Toxic Substances Management Policy considerations

During the review of Gavel® 75DF Fungicide and Zoxium® 80W Fungicide, the PMRA has considered the implications of the federal Toxic Substances Management Policy[1,2] and PMRA DIR99-03 and has concluded the following:

- It is not possible to determine if the TSMP criteria for persistence of Zoxamide and major transformation products is exceeded. The value for half-life of Zoxamide technical in soil (15 days) and water (21 days) is below the TSMP Track-1 cut-off criteria for soil and water (≥182 days). Zoxamide is unlikely to volatilize, based on its low vapour pressure. Therefore, a study of persistence in air is not triggered. Persistence of parent Zoxamide in the sediment and of the major transformation products in the field is unknown.

- Zoxamide is not bioaccumulative. Studies have shown that the *n*-octanol-water partition coefficient (log K_{ow}) is 3.76, which is below the TSMP Track-1 cut-off criterion of ≥5.0. Results of a bioaccumulation study with bluegill sunfish indicated that Zoxamide has a low potential to bioaccumulate. No evidence of accumulation of the parent compound or its metabolites was observed in the mammalian metabolism studies.

- The toxicity of Zoxamide is described in Chapters 3 and 6.

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1 The federal Toxic Substances Management Policy is available through Environment Canada's Web Site at: www.ec.gc.ca/toxics

2 The PMRA's Strategy for Implementing the Toxic Substances management policy, DIR99-03, is available through the Pest Management Information Service: Phone 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); Fax (613) 736-3798; E-Mail pminfoserv@hc-sc.gc.ca or through our website at www.hc-sc.gc.ca/pmra-arla

- Zoxamide does not contain any by-products or microcontaminants known to be Track-1 substances. Impurities of toxicological concerns are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

- The persistence, bioaccumulation and toxicity of the major transformation products RH-24549, RH-141288, RH-127450, and RH-139432 are unknown.

- The formulated product does not contain any formulants that are known to contain TSMP Track-1 substances.

8.1 Conclusions

The persistence of Zoxamide in sediment and the persistence, bioaccumulation and toxicity of the major transformation products RH-24549, RH-141288, RH-127450, and RH-139432 are unknown. Therefore, the potential for the entry of a TSMP Track-1 substance(s) into the environment, resulting from the use of Gavel® 75DF Fungicide and Zoxium® 80W Fungicide, cannot be determined at this time.

9.0 Regulatory decision

Zoxamide Technical and the end-use products Gavel® 75DF Fungicide and Zoxium® 80W Fungicide have been granted temporary registrations for use on potatoes and grapes, pursuant to Section 17 of the Pest Control Products Regulations, subject to the following conditions:

- submission of revised product specification form:

- submission of data on the potential for bioaccumulation in biota (*n*-octanol-water partitioning coefficient, K_{ow}) for major transformation products;

- submission of data on the persistence of Zoxamide in sediment and water system;

- submission of a study for the detection of inhalation sensitization potential;

- submission of freezer storage stability;

- product stewardship plan to ensure field worker notification and sensitization reactions reporting;

- monitoring data to determine resistance potential in potatoes;

- submission of efficacy data to establish the lowest efficacious rate for control of downy mildew on grapes by Gavel® 75DF Fungicide; and

- submission of product storage stability data.

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List of abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ALP	alkaline phosphatase
ARfD	acute reference dose
ATB	anti-tubulin benzamide
BCF	bioconcentration factors
bw	body weight
bwg	body-weight gain
CHO	Chinese hamster ovary
d	day(s)
DAT	days after treatment
DEEM™	Dietary Exposure Evaluation Model™
DF	dry flowable
DT_{50}	time required for 50% dissipation
EC_{25}	concentration effective against 25% of test organisms
EC_{50}	median effective concentration
ECD	electron capture detection
EEC	expected environmental concentration
EPA	United States Environmental Protection Agency
FOB	functional observational battery
F_1	1st generation offspring
GAP	good agricultural practice
GSD	geometric standard deviation
GC	gas chromatography
h	hour(s)
ha	hectare(s)
HPLC	high performance liquid chromatography
IPM	integrated pest management
K_{ow}	*n*-octanol-water partition coefficient
K*d*	adsorption quotient
K_{oc}	adsorption quotient normalized to organic carbon
lb(s)	pounds(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEL	lowest observable effect level
LOQ	limit of quantitation
MAS	maximum average score (at 24, 48 and 72 h)
MMAD	mass median aerodynamic diameter
MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue limit
MSD	mass selective detection
NAFTA	North American Free Trade Agreement

NOAEL	no observed adverse effect level
NOEC	no observable effect concentration
NOEL	no observable effect level
NZW	New Zealand White
P_1	first parental generation
PDI	potential daily intake
pH	$\log_{10}$ hydrogen ion concentration
PHED:	Pesticide Handlers Exposure Database
PHI	Pre-harvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RAC	raw agricultural commodity
ROC	residue of concern
SD	standard deviation
SF	safety factor
$t_{½}$	half-life
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
μg	microgram
μL	microlitre
UV	ultraviolet
WBC	white blood cell
WP	wettable powder

Appendix I Method of analysis

Table 1 Methods for analysis of the active substance as manufactured

Product	Analyte	Method	Recovery	SD	Method acceptability
Technical	Zoxamide	HPLC–UV	not required	0.56%	acceptable
	impurities	HPLC–UV and GC with flame ionization dection	83–130%	3.5–31%	acceptable

Table 2 Method for formulation analysis

Product	Analyte	Method	Mean recovery (%)	SD	Method acceptability
Zoxium® 80W Fungicide	Zoxamide	HPLC–UV at 210 nm (Method ID: 95-159-02)	99.7 (n = 5)	0.18 (n = 5)	acceptable
Gavel® 75DF Fungicide	Zoxamide	HPLC–UV at 210 nm (Method ID: 95-159-02)	not provided	0.26 (n = 6)	acceptable
	Mancozeb	CS_2 evolution	not required for accepted method		

Table 3 Methods for residue analysis

ANALYTICAL METHODS - PLANT AND ANIMAL MATRICES GC-ECD and GC-MSD (gas chromatography with mass selective detection) ROC: residue of Zoxamide per se 3,5-dichloro-N-(3-chloro-1-ethyl-1-methylacetonyl)-p-toluamide: in grapes and the combined residues of Zoxamide and its metabolites 3,5-dichloro-1,4-benzenedicarboxylic acid (designated by company code RH-141455 or RH 1455) and 3,5-dichloro-4-hydroxymethyl benzoic acid (RH-141452 or RH-1452) in potato.						
Matrix	Grape					
	grape	juice	raisins			
Limit of quantitation (LOQ)	0.01	0.01	0.01			
Recovery: mean (%) ± SD	91.5±15.8	average 109	average 107			
Matrix	potato (sum of three metabolites)					
	tuber	flakes	chips	peel		
Limit of quantitation (LOQ)	0.06	0.06	0.06	0.06		
Recovery: mean (%) ± SD	81.5 - 92.3 ±13.3 - 19	103 ± 13	93.2 ± 9.9	87 - 127		
Matrix	Dairy cattle & Poultry					
	Milk	Lean meat	Fat	Eggs	Liver	Kidney
Limit of quantitation (LOQ)	No methods submitted					
Recovery: mean (%) ± SD	Not applicable					

Appendix II Summary of the toxicity studies with Zoxamide

METABOLISM

Zoxamide was rapidly and extensively absorbed, metabolized and excreted by both sexes for all dosage regimens. Approximately 61% of administered dose was systemically absorbed. In the high dose group, large amounts of parent were observed in the feces, suggesting lesser absorption. Maximum plasma concentrations were reached approximately 8 h post dose. Residue concentrations were highest in organs associated with absorption (liver, stomach, intestines). Metabolism occurred by primary hydrolysis, glutathione mediated reactions, and reductive dehalogenation; secondary oxidation of the aromatic methyl and the aliphatic side chain; and terminal glucurionic acid and amino acid conjugations. No residues were detected in expired air. In urine and feces, parent and 35 metabolites were detected; 24 were identified. In the bile, 17 metabolites were detected; 13 were identified. No single metabolite, except parent, accounted for more than 10% of administered dose. Fecal and urinary metabolites were similar quantitatively and qualitatively between sexes. Based on comparison of single and repeat dosed animal, induction of metabolism (glutathione transferase and or glutathione cofactor) appeared to occur. Elimination from plasma was bi-phasic with an elimination half-life of 12-14 h in both low and high dose groups. Over 85% of the administered dose in single dose studies was excreted within 24- 48 h (74 - 92% in feces; 4 - 27% in urine). Biliary excretion was rapid (>50% of administered dose in 12 h) and accounts for 39% of the administered dose. Parent compound accounted for 12 - 23% (low dose) and 71 - 74% (high dose) of excreted residue. Tissue residues were low (0.04-0.17% of administered dose in tissues, 0.34 - 1.9% in carcass, 5 days post dose), suggesting accumulation does not occur.

The two major potato metabolites (RH-141452 and RH-141455), which were minor rat metabolites, were studied in separate metabolism studies. More than 97% of administered dose (RH-141452) was excreted within 24 h. Greater than 94% was eliminated unchanged in urine. Two glucuronide conjugates and a glycine conjugate (~3% of the administered dose) were found in urine. An additional 1.6% of the administered dose was excreted unchanged in the feces. Excretion of RH-141455 slower, 47% of the administered dose excreted within 24 h, an additional 32% of the administered dose between 24 and 48 h. Greater than 92% of the administered dose was recovered (about 73% in feces, 11% in urine, 9% cage rinse) as unchanged RH-141455 (>96%).

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
ACUTE STUDIES: Technical active			
Oral 95R-268 MRID 44731805	Rat Crl:CDBR 5000 mg/kg bw	LD_{50} >5000 mg/kg bw Limit dose	No deaths. Diarrhea and feces containing white material in a few rats by day 2. Red stained fur on eye or muzzle on a few rats.
Oral 98R-165 MRID 44731806	Mouse Crl:CD-1(ICR)BR 5000 mg/kg bw	LD_{50} >5000 mg/kg bw Limit dose	No deaths. No clinical signs. No gross pathology.
Dermal 95R-269 MRID 44731807	Rat Crl:CDBR 2000 mg/kg bw	LD_{50} >2000 mg/kg bw Limit dose	No treatment related deaths. Red stained fur on eyes or muzzle on a few rats. 1 ♂, 1 ♀ scant feces on day 2. Desiccation and reddened skin on several rats day 2 and days 6-8. No gross pathology.

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Inhalation 95R-266 MRID 44731808	Rat Crl:CDBR 0, 1.9, 5.3 mg/L (gravimetic concentration) mean mass aerodynamic diameter (MMAD) = 4.0-4.3 μm, GSD 2.2, 2.1 % respirable:	LC50 >5.3 mg/L Limit dose	No deaths. Red stained muzzle or eyes in 3 control and 5 HD mg/L rats. Recovery by day 1. No gross pathology.
Skin Irritation Rabbits 95R-270 MRID 44731810	Rabbit NZW 0.5 g	Non-irritant	No irritation noted on any rabbits. PII (maximum average score (MAS) 24, 48, 72 h)= 0
Eye Irritation 95R-271 MRID 44731809	Rabbit NZW 0.1 g	EPA: Moderately irritating PMRA: Mildly irritating	MAS (24, 48, 72 h) 15.2 All scores 0 on day 7. Corneal opacity observed, resolution by 72 h. EPA: Caution PMRA: Caution: Eye Irritant
Skin sensitization (Buehler method) 97R-074 MRID 44731812	Guinea pig Hartley female	Strong sensitizer	PMRA: Skin sensitizer Titration experiment: 100, 25, 7.5, 2.5, 0.75, 0.25% technical on patches Incidence of positive animals: 10/19, 9/10. 7/10, 8/10, 10/10, 7/10. Naive control 0/40. Grade of response in positive animals: 1-2. >15% incidence of sensitized animals defined as positive. Labelling required
Skin sensitization (Buehler method) 98R-154 MRID 44731813	Guinea pig Hartley male	Unacceptable study due to solvent change at challenge.	n/a
Skin sensitization (maximization test) 95RC-170 MRID 44731811	Guinea pig, albino Hra:(DH)fBR males	Strong ensitizer	PMRA: Skin sensitizer All exposed animals exhibited moderate to intense dermal reactions (grades 2-3). >30% incidence of sensitized animals defined as positive. Labelling required

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
ACUTE STUDIES: Metabolites of the technical active			
Oral 98R-049 MRID 44731834	Mouse Crl:CD-1(ICR)BR) 5000 mg/kg bw	LD50 >5000 mg/kg bw Limit dose **Metabolite RH-141452**	No treatment related deaths. 1 ♂ scant feces day 1 only. 1 ♂ brown and yellow anogenital staining, day 1 only. No gross pathology.
Oral 98R-047 MRID 44731837	Mouse Crl:CD-1(ICR)BR) 5000 mg/kg bw	LD50 >5000 mg/kg bw Limit dose **Metabolite RH-141455**	No deaths. No clinical signs. No gross pathology
ACUTE STUDIES: End Use Product Zoxium® 80W Fungicide			
Oral 97R-085 MRID 44732102	Rat Crl:CDBR 5000 mg/kg bw	LD50 >5000 mg/kg bw Limit dose	No deaths. No findings.
Dermal 97R-086 MRID 44732103	Rat Crl:CDBR mg/kg bw	LD50 >5000 mg/kg bw Limit dose	No deaths. Red stained fur on eye and muzzle (several rats persisted). Some animals passive, pale, scant feces; recovery by day 5. Skin desiccation on a few animals, persisted in two ♀ to study termination.
Inhalation (nose only) 97R-089 MRID 44732104	Rat Crl:CDBR 3.8 mg/L (gravimetric concentration) MMAD = 3.4 μm, GSD = 2.3	LC50 >3.8 mg/L Limit dose	1 death. The decedent had reddened lungs. Red stained fur on eye and muzzle (several rats). No other findings.
Skin irritation - Rabbits 97R-087 MRID 44732106	Rabbit NZW 0.5 g	EPA: Moderate irritant PMRA: Moderate irritant	PII (MAS 24, 48, 72 h): 3.2 Very slight to well denied erythema persisted to termination. Very slight to moderate edema at patch removal progressed to very slight to severe by 24 h; resolved by day 7. 5/6 rabbits showed dessication on day 7. Warning Skin Irritant Causes skin irritation. Do not get on skin.
Eye irritation 97R-088 MRID 44732105	Rabbit NZW 0.1 g	EPA: Moderate irritant. PMRA: Minimally irritating	MAS (24, 48, 72 h) 2.95 Corneal opacity resolved by 72 h. All effects resolved by 72 h. PMRA: Caution: Eye Irritant (upgraded based on opacity duration)

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Skin sensitization (Buehler method) 97R-090 MRID 44732107	Guinea pig Hartley female	Dermal sensitizer	Increasing irritation noted during induction phase. 9/20 positive animals. Irritation scores of 1. >15% incidence defined as positive. Labelling required.
ACUTE STUDIES: End use Product Gavel® 75DF Fungicide			
Oral 97R-062 MRID 44732133	Rat Crl:CDBR 5000 mg/kg bw	LD50 >5000 mg/kg bw Limit dose	No deaths. Passiveness, diarrhea, red material around the muzzle, scant faeces, soft faeces, respiratory noise, abnormal gait, thinness, low body posture, anogenital staining, tan faeces, and/or alopecia noted on some rats: recovery by day 10. Body weight gains about 36% below historical controls.
Dermal 97R-063 MRID 44732134	Rat Crl:CDBR 5000 mg/kg bw	LD50 >5000 mg/kg bw Limit dose	No deaths. Lacrimation (1/6), scant faeces (4/6) red stained fur on eyes/muzzle, desiccation and/or scabs on skin on several rats up to day 14.
Inhalation (nose only) 97R-066 MRID 44732135	Rat Crl:CDBR 5.1 mg/L (gravimetric concentration) MMAD = 5.6 ±0.2 μm, GSD = 2.3. 35% particles < 4 μm	LC50 >5.1 mg/L Limit dose	No deaths. No other treatment related findings. Author stated that it was not possible to generate an atmosphere with a MMAD of 4 μm or less.
Skin irritation - Rabbits 97R-064 MRID 44732137	Rabbit NZW 0.5 g	EPA: Slight irritant PMRA: Minimally irritating	PII (MAS 24, 48, 72 h): 0.39 Very slight to well defined erythema resolved by 72 h. Very slight edema resolved by 48 h. PMRA: No labelling required
Eye irritation 97R-065 MRID 44732136	Rabbit NZW 0.1 g	EPA: Moderate irritant PMRA: Minimally irritating	MAS (24, 48, 72 h): 13.8 Corneal opacity resolved by day 7. Iritis resolved by 48 h. Conjunctivitis resolved by day 7. PMRA: Caution: Eye irritant (upgraded based on opacity duration).

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Skin sensitization (Maximization method) 97R-067 MRID 44732138	Guinea pig Hartley female	Sensitizer	12/18 animals positive. Irritation scores of 1 and 2. >30% incidence defined as positive. Labelling required
SHORT-TERM TOXICITY Note: % values represent % of control			
28-d dermal toxicity 97R-075 MRID 44731818	Rat Crl:CDBR 0, 150, 400, 1000 mg/kg bw/d	NOAEL systemic = 1000 mg/kg bw/d Limit dose NOAEL dermal: not established LOAEL dermal: <150 mg/kg bw/d	♂ white blood cell (WBC) differential: lymphocytes ↓, neutrophils ↑ at 1000. ♀ WBC count ↑ at 1000. In ♀: albumin ↓, globin ↑ at 400, 1000; albumin/globin ratio ↓ all dose groups. Dermal affects all animals: scabbing ↑ incidence and ↑ in ♀ with dose. Histopathology of treated skin showed hyperplasia, hyperkeratosis, and inflammation. Changes seen in the dermis: hyperplastic sebaceous glands, mixed inflammatory cell infiltrations (mononuclear and polymorphonuclear leukocytes) and vasculitis / peri-vasculitis in deeper dermis. Technical material was not a dermal irritant in acute tests. The above skin reaction is likely a sensitization reaction.
90-d dietary - Mice 94R-075 MRID 44731814	Mouse Crl:CD-1(CR)BR VAF/+ 0, 70, 700, 2500, 7000 ppm ♀: 17, 174, 574, 1666 mg/kg bw ♂: 12, 123, 436, 1212 mg/kg bw	NOAEL ≥1666 mg/kg bw/d 7000 ppm Limit dose LOAEL not determined	No treatment related deaths No notable effects
90-d dietary toxicity / neurotoxicity 94R-233 MRID 44731815	Rat Crl:CDBR 0, 1000, 5000, 20000 ppm ♀: 80, 401, 1622 mg/kg bw/d ♂: 74, 372, 1509 mg/kg bw/d	NOAEL ≥1509 mg/kg bw/d Limit dose LOAEL not determined	No treatment related deaths. 1 high dose ♀ had lymphosarcoma (not considered treatment related). No effect on functional observation battery (FOB)

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
90-d dietary 96R-030 MRID 44731816	Dog Beagle 0, 1500, 7500, 30000 ppm ♀: 62, 322, 1055 mg/kg bw/d ♂: 55, 281, 1139 mg/kg bw/d	NOAEL ♀: 62 mg/kg bw/d ♂: 281 mg/kg bw/d LOAEL ♀: 321.6 mg/kg bw/d ♂: 1139 mg/kg bw/d	No treatment related deaths. **♀ at 321.6 (7500 ppm)** ↑ mean absolute and relative liver weight (23 / 27%) **♀ and ♂ at 1055/1139 (30000 ppm):** ↓ bw (18-21% at week 16), bwg (61-64% at week 16), total feed consumption (14-21%). At weeks 8 (♂) and 16 (♀): ↓ albumin (11-15%), albumin/globulin ratio (20-27%). ↑ abs/rel liver weight (22-35% / 55-63%) accompanied by diffuse hepatocellular hypertrophy. Thyroid follicular epithelium hypertrophy in 1 ♀ and 1 ♂ **♀ at 1055 (30000 ppm) at 8 and/or 16 weeks** ↓ RBC (10-15%), ↑ MCH(8-12%) and MCHC (3-6%). **♂ at 1139 (30000 ppm) at 16 weeks**, ↓lymphocytes (63%), ↑ neutrophils (48%).

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
12-month dietary 95R-277 MRID 44731817	Dog Beagle 0, 1500, 7500, 30000 ppm ♀: 0, 48, 278, 994 mg/kg ♂: 0, 50, 255, 1016 mg/kg	NOAEL 48 mg/kg bw/d (1500 ppm) LOAEL 255 mg/kg bw/d (7500 ppm)	No treatment related deaths. **♀ at 255 / 278 (7500 ppm):** ↓bw (-13%) and bwg (-57%) in first 4 weeks of study and persisted. ↑ incidence / animals involved of soft feces (8 days control vs 26 days) **♀ and ♂ at 2 55 / 278 (7500 ppm):** ↑ abssolute and relative liver weights (11-22%), ↑ thyroid weights(11-31%). ↑ ALP at 6, 12 months (♂:+125%, +106%; ♀: +42% at 6 months) **♀ at 994 (30000 ppm):** 1 animal raised focus on liver, 1 animal multi-focal necrosis in liver. **♀ and ♂ at 994 / 1016 (30000 ppm):** ↑ incidence / animals involved of soft feces. ↓ bwg (♀:-117% ;♂:-76%) in first 4 weeks of study and persisted. ↓bw (♂: -6%, ♀: -12%) at 52 weeks. ↓ food consumption (♂:-20, -25% ; ♀: -24, -19, -20%) during first 2-3 weeks. ↑ absolute and relative liver weights (22-48%), ↑ thyroid weights (28-50%). Diffuse hepatocyte hypertrophy in 1 ♀, 2 ♂.↑ ALP at 3, 6, 9, 12 months (at 6 and 12 months: ♂:+256%, +327%; ♀: +75%, +117%) There were no neoplastic lesions.
CHRONIC TOXICITY/ONCOGENICITY			
80-week (18 month) dietary 96R-094 96R-094A MRID 44731819	Mouse CD-1 0, 350, 1750, 7000 ppm ♀: 60, 326, 1289 mg/kg bw/d ♂: 51, 251, 1021 mg/kg bw/d	Chronic toxicity: LOAEL: not determined NOAEL ≥1289 mg/kg bw/d Limit dose Oncogenic potential: No oncogenic response at the doses tested.	In ♀ only, a non-significant trend for ↑ bronchioalveolar adenomas was observed. The maximal incidence was within historical control. When combined with bronchioalveolar carcinomas, there was no statistical significance.

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
2-year dietary 94RC-236 94RC-236A MRID 44731821	Rat Sprague Dawley (Crl:CDBR) 0, 1000, 5000, 20000 ppm ♀: 65, 328, 1331 mg/kg bw/d ♂: 51, 260, 1058 mg/kg bw/d	Chronic toxicity: LOAEL: not determined. NOAEL ≥1331 mg/kg bw/d Limit dose Oncogenic potential: No oncogenic response at the doses tested.	At interim sacrifice only, relative liver weight ↑ in ♀ at 328, 1331 mg/kg bw.
REPRODUCTION / DEVELOPMENTAL TOXICITY			
Multi-generation - Rat 95R-272 MRID44770001	Rat Crl:CDBR 0, 1000, 5000, 20000 ppm mg/kg bw/d: P_1♀: 82, 409, 1624 P_1♂: 71, 360, 1474 F_1♀: 108, 534, 2239 F_1♂: 100, 489, 2091	Parental LOAEL 1624 mg/kg bw/d NOAEL 409 mg/kg bw/d Offspring LOAEL: Not determined. NOAEL≥2091 mg/kg bw/d Limit dose Reproductive LOAEL: Not determined. NOAEL:≥2091 mg/kg bw/d Limit dose	♀ at 1624 (20000 ppm): ↓bwg in P (-12%) during pre-mating; ↓bw in F_1(-6-16%) during pre-mating. ↓food efficiency during pre-mating (-6-7%) P and F_1. ↑Liver weights (absolute and relative) in mid dose (7-8%) and high dose (12-13%) P_1 only, no histopathology.
Teratogenicity (gavage) 97R-079 MRID44731823	Rat Crl:CDBR 0, 100, 300, 1000 mg/kg bw/d	Maternal LOAEL: Not determined. NOAEL ≥1000 mg/kg bw/d Developmental LOAEL: Not determined. NOAEL ≥1000 mg/kg bw/d Limit dose Not teratogenic.	No effects. Not teratogenic.
Teratogenicity (gavage) 95R-267 MRID 44731824	Rabbit NZW 0, 100, 300, 1000 mg/kg bw/d	Maternal LOAEL: Not determined. NOAEL ≥1000 mg/kg bw/d Developmental LOAEL: Not determined. NOAEL ≥1000 mg/kg bw/d Limit dose Not teratogenic.	No effects. Not teratogenic.

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
GENOTOXICITY			
Bacterial reverse mutation assay (Ames Test) 96R-262 MRID 44731825	Salmonella typhimurium his - TA98, TA100, TA1535, TA1537, TA102	50, 200, 500, 2000, 5000 μg/plate Technical Zoxamide	Negative (±S9)
In vitro mammalian gene mutation at HGPRT locus 94RC-077 MRID 44731826	CHO culture	Range: Trial 1: 5 - 65 μg/mL / -S9 Trial 1: 2 - 55 μg/mL / +S9 Trial 2: 20 - 50 μg/mL / -S9 Trial 2: 25 - 55 μg/mL / +S9 Technical Zoxamide	Negative (±S9) Non-mutagenic at the HGPRT locus in CHO cells.
In vitro mammalian cytogenetics (chromosomal aberration) 96RC-125 MRID 44731827	CHO culture	Range: 0.9689 - 100 μg/mL ± S9 Technical Zoxamide	No structural chromosome aberrations up to the limit of toxicity, both in the presence and absence of S9. Increased numerical aberrations, both in the presence and absence of S9.
In vivo mammalian cytogenetics (micronucleus assay) 95R-264 MRID 44731828	Mouse CD-1	200, 1000, 2000 mg/kg bw Technical Zoxamide	Negative
Bone marrow distribution 97R-173 MRID 44731830	Mouse CD-1	2000 mg/kg bw Technical Zoxamide	Zoxamide equivalents distribute to mouse bone marrow, reaching concentrations of 5 - 55 ppm (μg/g bone marrow)
Bacterial reverse mutation assay (Ames test) 98R-050 MRID 44731835	*S. typhimurium* (his -) TA98, TA100, TA1535, TA1537, TA102	50, 200, 500, 2000, 5000 μg/plate **Metabolite: RH-141452**	Negative (±S9)
Bacterial reverse mutation assay (Ames Test) 98R-048 MRID 44731838	*S. typhimurium* (his -) TA98, TA100, TA1535, TA1537, TA102	50, 200, 500, 2000, 5000 μg/plate **Metabolite: RH-141455**	Negative (±S9)

STUDY	SPECIES OR STRAIN AND DOSES	NOEL OR NOAEL AND LOEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
SPECIAL STUDIES			
Acute neurotoxicity 95R-182 MRID44731831	Rat Crl:CDBR 0, 123, 485, 1976 mg/kg bw/d	LOAEL: Not determined. NOEL ≥1976 mg/kg bw/d Limit dose	No treatment related deaths. No effect on FOB No neuropathology.
90-day dietary toxicity and neurotoxicity 94R-233 MRID 44731815	Rat Crl:CDBR 0, 1000, 5000, 20000 ppm ♀: 80, 401, 1622 mg/kg bw/d ♂: 74, 372, 1509 mg/kg bw/d	LOAEL: Not determined. NOAEL ≥1509 mg/kg bw/d Limit dose	No treatment related deaths. 1 high dose ♀ had multi-centric lymphosarcoma (not considered treatment related). No effect on FOB.
Mechanism of action 98R-1098 MRID	The ATB compounds RH-117281 and RH-54032 inhibited nuclear division in the Oomycete fungus Phytophthora capsici by disruption of cellular microtubules as the result of a highly specific covalent binding to the β-subunit of tubulin. In vitro microtubule assembly assays demonstrated an inhibition of assembly by RH-117281 and RH-54032, which was unusual in requiring a prolonged incubation with tubulin. RH-117281 was comparable in potency to carbendazim in inhibiting microtubule assembly and the growth of mouse lymphoma cells, and was considerably less active than colchicine and vinblastine. Consistent with whole cell labelling experiments, the binding of radiolabelled RH-54032 to isolated bovine tubulin was shown to involve the β-subunit. In addition, non-specific binding, assumed to be covalent due to assay conditions, was shown to other proteins in the mouse lymphoma cell assay. Since binding of radiolabelled RH-54032 to isolated tubulin was strongly inhibited by colchicine, podophyllotoxin and nocodazole, but not by vinblastine, it appears likely that the ATBs bind at or near the colchicine binding site of tubulin.		

Compound-Induced Mortality:
Mortality was NOT identified as a compound-induced effect in short-term and long-term and special studies.

Recommended ARfD: NONE RECOMMENDED.

Recommended ADI: $\frac{\text{48 mg/kg bw/day (NOAEL)}}{\text{100 (UF)}}$ = 0.48 mg/kg bw

Based on chronic dog study. LOAEL of 255 mg/kg bw/d (7500 ppm) based on decreased bw, bwg, food consumption, increased absolute and relative liver weights, serum ALP and thyroid weights.

MOE for other critical endpoint(s): n/a

Appendix III Residues

PROPOSED CANADIAN USE PATTERN							
		Method and timing	Rate kg a.i./ha	Numbe per season	Maximum rate kg a.i./ha	PHI (days)	Restrictions
Potato	Gavel® 75DF Fungicide	foliar	0.187	6	1.122	3	none
	Zoxium® 80W Fungicide	foliar	0.187	6	1.122	3	none
Grape	Gavel® 75DF Fungicide	foliar	0.187	6	1.122	66	none
	Zoxium® 80W Fungicide	foliar	0.224	8	1.8	14	none

PLANT METABOLISM AND ANIMAL METABOLISM

Approximately 90% of the TRRs in grapes were characterized and identified. Zoxamide was identified as the major residue component. Approximately 85% of the total radioactivity found in potato tubers was characterized and identified. The principal metabolites identified in tubers were RH-1455 and RH-1452; parent Zoxamide was not detected.

ROC defined as product: residue of Zoxamide per se 3,5-dichloro-N-(3-chloro-1-ethyl-1-methylacetonyl)-p-toluamide: in grapes and the combined residues of Zoxamide and its metabolites 3,5-dichloro-1,4-benzenedicarboxylic acid (designated by company code RH-141455 or RH 1455) and 3,5-dichloro-4-hydroxymethyl benzoic acid (RH-141452 or RH-1452) in potato.

Matrix	PHI	TRRs [uniformly ring labelled], ppm	TRR's [Position 2-label], ppm
Potato-tuber	14	0.178	Not applicable
Grape-fruit	26-28	0.735	Not applicable

ANIMAL METABOLISM

Overall, 85-92% of the TRR in milk and tissues was adequately identified or characterized. Parent Zoxamide was not detected in any goat tissues or milk. In milk, M12a and M12b were the major residues, together accounting for 38% of the TRR. Other metabolites identified in milk included RH-141288, RH-127450, and RH-141454, each accounting for 12-20% of the TRR. In fat, RH-127450 accounted for the majority of the residue at 65% of the TRR, and RH-141288 was also identified at 16% of the TRR. In liver, seven polar metabolites identified mainly as glucuronic acid conjugates of hydroxylated parent residues comprised the major residues. The metabolic profile of kidney and muscle was similar to that of liver. At least five additional metabolites were detected in minor amounts in both kidney and muscle.

Matrix	% of administered dose (ppm)	
Goat	14C (uniform phenyl label)	
Tissues	0.5 (1.1)	
Milk	0.3 (0.236)	
Blood	not reported	
Feces	36.1	
Urine	40.9	

CONFINED CROP ROTATION STUDIES
2.0 kg ai/ha (1.1× gap); one foliar application post-emergent

Crop	Crop fraction	Planting interval (days after treatment, DAT)	Harvest Interval (DAT)	Equivalent to position 1 -14C-Zoxamide TRRs (ppm)
Mustard	leaves	30, 145, 210, 368	92, 255, 308, 423	<0.01 - 0.041
Radish	leaves, roots	30, 210, 368	92, 255, 423	0.011 - 0.048
Sorghum	forage, stover, grain	31, 210, 368	70, 238, 336, 406, 504	<0.01 - 0.05
Wheat	forage, grain	138	279, 368	<0.01
Soybean	forage, hay, grain	31, 210, 368	70, 179, 238, 362, 406, 530	0.012 - 0.189
Turnips	leaves, roots	138	308	<0.01 - 0.042

ANALYTICAL METHODS: PLANT AND ANIMAL MATRICES
GC-ECD and GC-MSD
ROC: residue of Zoxamide per se 3,5-dichloro-N-(3-chloro-1-ethyl-1-methylacetonyl)-p-toluamide: in grapes and the combined residues of Zoxamide and its metabolites 3,5-dichloro-1,4-benzenedicarboxylic acid (designated by company code RH-141455 or RH 1455) and 3,5-dichloro-4-hydroxymethyl benzoic acid (RH-141452 or RH-1452) in potato.

Matrix	Grape					
	grape	juice	raisins			
Limit of quantitation (LOQ)	0.01	0.01	0.01			
Recovery: mean (%) ± SD	91.5±15.8	average 109	average 107			

Matrix	potato (sum of three metabolites)					
	tuber	flakes	chips	peel		
Limit of quantitation (LOQ)	0.06	0.06	0.06	0.06		
Recovery: mean (%) ± SD	81.5 - 92.3 ±13.3 - 19	103 ± 13	93.2 ± 9.9	87 - 127		

Matrix	Dairy cattle and Poultry					
	Milk	Lean meat	Fat	Eggs	Liver	Kidney
Limit of quantitation (LOQ)	No methods submitted					
Recovery: mean (%) ± SD	Not applicable					

FREEZER STORAGE STABILITY TESTS
Stability of residue of Zoxamide at -20°C for 0 - 17.5 months.
Plant metabolism and residue samples were stored within the time periods studied.

Storage interval (months) Grapes	Spiking level (ppm) parent only	Freshly spiked % Residues recovered			Stored spiked % Residues recovered		
		grape	juice	raisin	grape	juice	raisin
0-17.5 Months	0.09-0.94	90	99	78	75-159	52-96	57-140
Storage Interval (months) POTATO	Spiking level (ppm) parent plus two metabolites	Freshly spiked % residues recovered			Stored spiked % residues recovered		
		tuber	flakes	chips	tuber	flakes	chips
2 - 11 Months	0.06-0.86	95-128	none	none	107-144	none	none

FREEZER STORAGE STABILITY TESTS
Stability of Zoxamide residues in meat, milk, eggs substrates.
Animal metabolism and residue samples were stored within the time periods studied.

Storage interval (months)	Freshly spiked % residues recovered				Stored spiked % residues recovered			
	Beef liver	Milk	Poultry breast	Eggs	Beef liver	Milk	Poultry breast	Eggs
	None submitted							

SUPERVISED RESIDUE TRIALS ON GRAPES AND POTATO

Commodity and portion analysed	Formulation	Application			PHI (days)	Residues (ppm)
		No.	Total Rate kg a.i./ha	% gap		
Grape	Either Gavel® 75DF Fungicide or Zoxium® 80W Fungicide	10	1.4-4.48	80-250	14	1.2-4.5
Potato tuber		10	1.4-2.8	110-200	3	< 0.06

PROCESSING STUDIES - Residue Levels of Zoxamide in grapes and potato and processed fractions

Matrix and fraction	Rate kg a.i./ha	PHI (days)	Residues in RAC (ppm)	Concentration factor
Grape juice - clarified	1.4-2.8	14	0.313 - 0.393	0.05×
Grape juice - unclarified			0.313 - 0.393	0.10×
Grape raisins			0.313 - 0.393	6.97× theoretical factor is 4.7×

PROCESSING STUDIES - Residue Levels of Zoxamide in grapes and potato and processed fractions				
Matrix and fraction	Rate kg a.i./ha	PHI (days)	Residues in RAC (ppm)	Concentration factor
Potato chips	11.2	3	0.047	1.2×
Potato flakes			0.047	3.98×

CATTLE FEEDING STUDY
None submitted due to no expectation of finite residues in animal products. Dietary burden was 0.6 and 0.3 ppm for beef and dairy cattle, respectively.

Feeding level (ppm)	Maximum product ×2 residues (ppm)			
	Milk	Tissues	Fat	Blood
5 (40×)	No feeding study was submitted. No expectation of finite residues in animal commodities			
25 (200×)				
50 (400×)				

HEN FEEDING STUDY
None submitted as there are no feed items for poultry associated with this petition.

Feeding level (ppm)	Eggs	Tissues	Fat	Blood
0.1 (2×)	None submitted as there are no feed items for poultry associated with this petition			
0.5 (10×)				
1.0 (20×)				

PROPOSED MRLs

Crop	Proposed MRLs or tolerances resulting from the joint review of Zoxamide	
	Canada (ppm)	U.S. (ppm)
Grapes	3	3
Raisins	15	15
Potatoes	0.06	0.06
Potato: flakes and granules	0.3	0.3
Potato: wet peel	Not applicable	0.1

CHRONIC DIETARY RISK ASSESSMENT using DEEM Software based on the 1994-1998 Continuing Survey of Food Intake by Individuals
ADI = 0.48 mg/kg bw; Tier I: Using the proposed MRLs and a default value of 10% for water

	Total population	All infants (< 1 year)	Children (1-6 years)	Children (7-12 years)	Female (13-50 years)	Male (20+ years)	Seniors (55+ years)
% of ADI	10.4	10.5	11.4	10.5	10.2	10.2	10.3

Appendix IV Environmental assessment

Table 1 Summary of terrestrial fate data

Fate process	Endpoint	Interpretation
Hydrolysis	t½ at pH 4: 15.5 d t½ at pH 7: 15.7 d t½ at pH 9: 8.1 d	Hydrolysis will be an important route for transformation or dissipation of Zoxamide in the terrestrial environment.
Phototransformation	DT_{50} = 7 d on soil, primarily due to microbial and/or hydrolytic processes	Phototransformation will not be a route for transformation or dissipation of Zoxamide on soil.
Aerobic biotransformation	DT_{50}= 7 - 14 d in soil	Zoxamide is classed as non-persistent to slightly persistent in soil under aerobic conditions.
Anaerobic biotransformation	DT_{50}= 15 d in soil	Zoxamide is classed as slightly persistent in soil under anaerobic conditions.
Adsorption and desorption	Adsorption K_{oc}= 814 - 1431 mL/g carbon Desorption K_{oc}= 927 - 1671 mL/g carbon	Zoxamide has a low potential for mobility in the soil.
Aged soil column leaching	No studies submitted	-
Field dissipation and leaching	DT_{50}= 4.6 - 15 d No residues of parent compound and transformation products below the 7.5 cm soil depth	Zoxamide is non-persistent in soil under field conditions. Zoxamide did not leach appreciably under conditions of the field study.

Table 2 Summary of aquatic fate and transformation data

Fate process	Endpoint	Interpretation
Hydrolysis	t½ at pH 4: 15.5 d t½ at pH 7: 15.7 d t½ at pH 9: 8.1 d	Hydrolysis will be an important route for transformation or dissipation of Zoxamide in the aquatic environment.
Phototransformation	DT_{50} = 15.7 d in water	Phototransformation may be a route for transformation or dissipation of Zoxamide in the photic zone of clear natural water.
Aerobic biotransformation	DT_{50} = 6 - 21 d in water	Zoxamide is classed as non-persistent to slightly persistent in water under aerobic conditions.
Adsorption and desorption	Adsorption K_{oc}= 814 - 1431 mL/g carbon Desorption K_{oc}= 927 - 1671 mL/g carbon	Zoxamide has a potential for partitioning into the sediment.
Field dissipation	No study submitted	-

Table 3 Summary of terrestrial fate and transformation data

Fate process	Major transformation products (percent of applied Zoxamide)	Minor transformation products (percent of applied Zoxamide)
Hydrolysis	RH-150721 (37.6 % at pH 4) RH-24549 (30.9 % at pH 4) RH-141288 (50.2 % at pH 9) RH-129151 (24.5 % at pH 7)	Nine minor transformation products found, with concentrations ≤ 5 % of parent applied
Phototransformation on soil	RH-24549 (22 %) RH-127450 (11 %)	Dihydroxy product (6.73 %)
Phototransformation in water	RH-150721 (15 %) RH-24549 (27.7 %) RH-139432 (42.4 %)	None found
Aerobic biotransformation in soil	RH-139432 (≥10 %) RH-24549 (≥10 %)	None found
Anaerobic biotransformation in soil	RH-24549 (≥10 %) RH-127450 (≥10 %)	Nine minor transformation products found, with concentrations ≤5 % of parent applied
Aerobic biotransformation in sediment and water	RH-127450 (≥10 %) RH-163353 (≥10 %)	None found
Terrestrial field dissipation	Major transformation products not characterized	Minor transformation products not characterized

Table 4 The maximum EECs of Zoxamide on vegetation and other food sources immediately following application at the Canadian maximum label rate of 750 g a.i./ha.

Environmental compartment	Concentration fresh weight (mg a.i./kg)[a]	fresh weight / dry weight ratio	Concentration dry weight (mg a.i./kg)
short range grass	160.5	3.3[b]	530
leaves and leafy crops	84	19[b]	924
long grass	73.5	4.4[b]	323.4
forage crops	90	5.4[b]	486
small insects	39	3.8[c]	148.2
pods with seeds	8	3.9[c]	31.3
large insects	6.7	3.8[c]	25.36
grain and seeds	6.7	3.8[c]	25.36
fruit	10.05	7.6[c]	76.4

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973).

[b,c] Fresh weight to dry weight ratios from [b]Harris (1975) and [c]Spector (1956).

Table 5 Summary of toxicity of Zoxamide to terrestrial organisms

Group	Organism	Study	NOEL or NOEC	LD_{50}, LC_{50} or EC_{25}	Degree of toxicity
Birds	bobwhite quail	acute oral	2000 mg a.i./kg bw	> 2000 mg a.i./kg body weight	practically non-toxic
	bobwhite quail	dietary	5250 mg a.i./kg diet	> 5250 mg a.i./kg diet	practically non-toxic
	mallard duck	acute oral	not determined	not determined	-
	mallard duck	dietary	2625 mg a.i./kg diet	> 5250 mg a.i./kg diet	practically non-toxic
	bobwhite quail	reproduction	1000 mg a.i./kg diet	> 1000 mg a.i./kg diet	no significant treatment-related effects
	mallard duck	reproduction	1000 mg a.i./kg diet	> 1000 mg a.i./kg diet	no significant treatment-related effects
Mammals	rat	acute oral	not determined	> 5000 mg a.i./kg bw	practically non-toxic
	rat	dermal	not determined	> 2000 mg a.i./kg bw	low toxicity
	rat	inhalation	not determined	> 5.3 mg a.i./L	low toxicity
	beagle dog	subchronic oral	62 mg a.i./kg bw/d for females	not determined	toxic
	rat	2 generation reproduction	2091 mg a.i./kg bw/d	not determined	no adverse treatment-related effects
Soil organisms	earthworm	acute	66.7 mg a.i./kg soil	> 1070 mg a.i./kg soil	low toxicity
Beneficial arthropods	honey bees	acute oral	not determined	> 100 μg a.i./bee	non toxic
Terrestrial plants	phytotoxicity	Pre- or post-emergent applications of up to 500 g a.i./ha did not cause chlorosis, necrosis, malformations or growth inhibition in 17 crop species tested: corn, cotton, wheat, rice, barley, cabbage, carrots, lettuce, melon, onion, peas, rape, rye, sugar beets, sunflower, tomato and soybean.			

Table 6 Summary of risk assessment for terrestrial organisms

Organism	Effect	NOEC or NOEL	EEC	Margin of safety	Risk	Mitigative measures
Bobwhite quail	reproductive	1000 mg a.i./kg diet	0.95 mg a.i./d	16	low	not required
Mallard	reproductive	1000 mg a.i./kg diet	5.66 mg a.i./d	9	low	not required
Eastern cottontail	acute (rat study)	LD_{50} >5000 mg/kg bw	23.3 mg a.i./d	-	low	not required
Masked shrew	acute (rat study)	LD_{50} >5000 mg/kg bw	37.05 - 111.15 mg a.i./d	-	low	not required
Meadow vole	acute (rat study)	LD_{50} >5000 mg/kg bw	78.7 - 127.2 mg a.i./d	-	low	not required
Earthworm	acute	no data submitted	-	-	-	-
Honeybees	acute contact	> 100 μg a.i./bee	0.92 g a.i./kg	> 20000	low	not required

Table 7 Summary of toxicity of Zoxamide to aquatic organisms

Group	Organism	Study	NOEC	LC_{50}, EC_{50} or EC_{25}	Degree of toxicity
Fish	rainbow trout	acute	51 μg a.i./L	156 μg a.i./L	highly toxic
	bluegill sunfish	acute	not determined	>790 μg a.i./L	highly toxic
	rainbow trout	early life-stages	3.48 μg a.i./L	-	highly toxic
	fathead minnow	full life cycle	60 μg a.i./L	-	highly toxic
	sheepshead minnow	acute	860 μg a.i./L	>860 μg a.i./L	moderately toxic
	sheepshead minnow	early life-stages	40 μg a.i./L	-	highly toxic
Invertebrates	water flea	acute	780 μg a.i./L	>780 μg a.i./L	highly toxic
	water flea	chronic	39 μg a.i./L	85 μg a.i./L	highly toxic
	chironomid midge	chronic	210 μg a.i./L	-	highly toxic
	saltwater mysid	acute	17 μg a.i./L	75 μg a.i./L	highly toxic
	saltwater mysid	chronic	7.2 μg a.i./L	-	highly toxic

Group	Organism	Study	NOEC	LC_{50}, EC_{50} or EC_{25}	Degree of toxicity
	oyster shell-deposition	acute	123 µg a.i./L	715 µg a.i./L	highly toxic
Algae	blue-green alga	acute	4.1 µg a.i./L	23 µg a.i./L	highly toxic
	green alga	acute	860 µg a.i./L	>860 µg a.i./L	highly toxic
	green alga	acute	7 µg a.i./L	10 µg a.i./L	highly toxic
	freshwater diatom	acute	210 µg a.i./L	>930 µg a.i./L	highly toxic
	marine diatom	acute	490 µg a.i./L	>910 µg a.i./L	highly toxic
Plants	duckweed	acute	9 µg a.i./L	19 µg a.i./L	highly toxic

Table 8 Summary of risk assessment for aquatic organisms

Organism	Effect	NOEC or NOEL (µg a.i/L)	EEC (µg a.i./L) (overspray scenario)	MOS	Risk	Mitigative measures
Water flea	acute	780	310	2.5	low	buffer zone
	chronic	39	310	0.12	moderate	buffer zone
Saltwater mysid	chronic	7.2	310	0.02	high	buffer zone
Fish: Rainbow trout	acute	51	310	0.16	moderate	buffer zone
	early life-stages	3.48	310	0.01	high	buffer zone
Green algae	acute	4.1	310	0.01	high	buffer zone
Duckweed	acute	9	310	0.03	high	buffer zone

Appendix V Efficacy and sustainability summary tables

Table 1 Summary of Gavel® 75DF Fungicide label proposals and recommendations

Proposed		Recommendation (based on value assessment)	Comments
Gavel® 75DF Fungicide on potatoes			
Timing and number of applications	Make up to 10 applications every 5-7 d under high disease pressure and every 7-10 d under low disease pressure. Use low rate early in the season and high rate after row closure.	Make up to 6 applications every 7 d.	Data support a 7 d application interval only with rate based on disease pressure not growth stage.
Application methods	Ground, air or chemigation	Product not to be applied by chemigation.	For ground and aerial application only. Add the dilution rate for aerial application on potatoes.
Pest	Late blight, tuber rot, early blight	Tuber rot not acceptable for registration	Delete tuber rot from label.
Application rate	1.7 - 2.25 kg/ha	Same	Same
Resistance management	None	Formulated mix considered to be sufficient.	Add standard resistance management statements according to DIR99-06.
Gavel® 75DF Fungicide on grapes			
Timing and number of applications	Make up to 6 applications starting when new shoots are 1 - 4 cm long, repeat at 8 - 12 cm and at 20 - 25 cm. Continue applications on a 7 - 10 d interval when conditions are favourable to disease development.	Same	Same
Application methods	Ground, air or chemigation	Product is not to be applied by air and chemigation.	For ground application only
Pest	Downy mildew and black rot	Black rot not acceptable for registration	Delete black rot from label.
Application rate	2.25 - 2.8 kg/ha	Data support 2.25 kg/ha only	Delete 2.8 kg/ha from label
Resistance management	None	Formulated mix considered to be sufficient	Add standard resistance management statements according to DIR99-06

Table 2 Summary of Zoxium® 80W Fungicide label proposals and recommendations

Proposed		Recommendation (based on value assessment)	Comments
Zoxium® 80W Fungicide on potatoes			
Timing and number of applications	Make up to 10 applications every 5-7 d with low rate early in the season and high rate after row closure.	Make up to 6 applications every 7 d.	Data support a 7 d application interval only with rate based on disease pressure not growth stage.
Application methods	Ground, air or chemigation	Product is not to be applied by chemigation	For ground and aerial application only. Add the dilution rate for aerial application on potatoes.
Pest	Late blight, tuber rot, early blight	Tuber rot not acceptable for registration	Delete tuber rot from label.
Application rate	175 - 235 g/ha	Use of Zoxamide applied alone is not acceptable for registration. Only the tankmix with Mancozeb can be supported	Add instructions for tankmixing with Mancozeb to the label. 175 g Zoxium® 80W Fungicide + 1.5 kg Dithane® DG Rainshield NT Fungicide, 235 g Zoxium® 80W Fungicide + 2.0 kg Dithane® DG Rainshield NT Fungicide
Resistance management	None	Tankmix considered to be sufficient	Add standard resistance management statements according to Dir99-06
Zoxium® 80W Fungicide on grapes			
Timing and number of applications	Make up to 8 applications starting when new shoots are 1 - 4 cm long, repeat at 8 - 12 cm and at 20 - 25 cm. Continue applications on a 7 to 10 d interval when conditions are favourable for disease development.	Same	Same
Application methods	Ground, air or chemigation	Product is not to be applied by air and chemigation.	For ground application only
Pest	Downy mildew, powdery mildew and black rot	Same	Same
Application rate	175 - 280 g/ha	Same	Same
	Tankmix with Nova® 40W Fungicide at label rate	Same	Same

Resistance *management*	Alternate with a fungicide having a different mode of action after 3 applications.	Alternate after 2 applications.	Modify the alternation statement to "...after two sequential applications." Add standard resistance management statements according to DIR99-06.

Table 3 Survey of alternatives: potatoes late blight

Technical grade active ingredient TGAI + CODE	Fungicide Classification		End-Use Products maximum of three per active ingredient	Mix type[b]	Application rate
	Group	Mode of Action			
Captan CAP	M	Multi-site activity	Maestro 75DF	n/a	1987 - 3000 g a.i./ha
			Maestro 80DF	n/a	2000 - 3000 g a.i./ha
Copper sulphate CUB	M	Multi-site activity	Copper 53W	n/a	2915 g a.i./ha
			Griffin Basicop	n/a	2120 - 3710 g a.i./ha
Copper oxychloride CUY	M	Multi-site activity	Gardsman Copper Oxychloride	n/a	2000 g a.i./ha
			Fixed Copper 50W	n/a	2250 g a.i./ha
			Clean Crop Copper Spray	n/a	2750 g a.i./ha
Copper hydroxide CUZ	M	Multi-site activity	Kocide 101	T	550 - 1120 g CUZ/ha + 1400 - 1800 g MCZ /ha
			Kocide DF	T	675 - 1040 g CUZ /ha + 1400 - 1800 g MCZ /ha
			Parasol Wettable Powder	T	550 - 1250 g CUZ /ha + 1400 - 1800 g MCZ /ha
Cymoxanil CYO		Inhibition of nucleic acid and protein synthesis	Curzate 60 DF	F	135 CYO + 1280 MCZ g a.i./ha
Dimethomorph DME	15 + M[a]	Interference with cell wall forming process + Multi-site activity	Acrobat MZ	F	150 DME + 1500 MCZ g a.i./ha
Anilazine DYR	M	Multi-site activity	Dyrene 50WP	n/a	938 - 3281 g a.i./1000 L

Technical grade active ingredient TGAI + CODE	Fungicide Classification		End-Use Products maximum of three per active ingredient	Mix type[b]	Application rate
	Group	Mode of Action			
Maneb MAN	M	Multi-site activity	Dithane® M-22 Fungicide 80% WP	n/a	880 - 1800 g a.i./ha
			Maneb 80W	n/a	1800 g a.i./ha
			Maneb 75DF	n/a	863 - 1800 g a.i./ha
Mancozeb MCZ	M	Multi-site activity	Dithane® M-45 Fungicide 80WP	n/a	880 - 1800 g a.i./ha
			Dithane® DG Rainshield NT Fungicide	n/a	825 - 1688 g a.i./ha
			Pencozeb 75DF	n/a	825 - 1688 g a.i./ha
Metalaxyl-M MFN	4 + M	RNA synthesis + Multi-site activity	Ridomil Gold MZ 68WP	F	90 MFN + 1440 MCZ g a.i./ha
	4 + M	RNA synthesis + Multi-site activity	Ridomil Gold/Bravo Twin-Pak	F	
Metiram MTR	M	Multi-site activity	Polyram 80W	n/a	880 - 1800 g a.i./ha
			Polyram DF	n/a	880 - 1800 g a.i./ha
			Polyram 16 Dust	n/a	1920 - 2240 g a.i./ha
Propamocarb HCl PHY	U + M	Unknown + Multi-site activity	Tattoo C	F	1012 PHY+ 1012 TET g a.i./ha
Chlorothalonil TET	M	Multi-site activity	Bravo 500	n/a	600 - 1200 g a.i./ha
			Bravo Ultrex 90 SDG	n/a	630 - 1170 g a.i./ha
Zineb ZIN	M	Multi-site activity	Zineb 80W	n/a	1360 - 2640 g a.i./ha
			Dithane® Z-78 Fungicide	n/a	1688 - 2813 g a.i./ha
			Zineb 80W	n/a	1600 - 2400 g a.i./ha

[a] The second group refers to the other active present in the formulation (see application rate).

[b] Mix type refers to formulated mixture (F) or tankmix (T)

Table 4 Survey of alternatives: grapes downy mildew

Technical grade active ingredient TGAI + CODE	Fungicide classification		End-use products maximum of three per active ingredient	Mix type[b]	Application rate
	Group	Mode of action			
Azoxystrobin AZY	11	Inhibition of mitochondrial respiration	Abound Flowable	n/a	200 - 250 g a.i./ha
			Abound Fungicide	n/a	200 - 250 g a.i./ha
Captan CAP	M	Multi-site activity	Captan 50-W	n/a	1625 - 2750 g a.i./ha
			Captan 80W	n/a	1600 - 2800 g a.i./ha
Copper sulfate CUB	M	Multi-site activity	Griffin Basicop Fungicide	n/a	1590 g a.i. per 1000 L
Copper oxychloride CUY	M	Multi-site activity	Gardsman Copper Oxychloride 50WP Fungicide	n/a	1500 - 3000 g a.i. per 1000 L
			Fixed Copper 50-W	n/a	1500 - 3000 g a.i. per 1000 L
			Clean Crop Copper Spray	n/a	1500 - 3000 g a.i. per 1000 L
Dinocap DIN	U	Unknown	Dikar® WP Fungicide	F	253 DIN+ 3960 MCZ g a.i./ha
Folpet FOL	M	Multi-site activity	Folpan 50 WP	n/a	1000 g a.i. per 1000 L
Mancozeb MCZ	M	Multi-site activity	Dithane® M-45 Fungicide	n/a	5400 g a.i./ha
			Manzate 200WP	n/a	5400 g a.i./ha
			Penncozeb 80WP	n/a	5400 g a.i./ha
Metalaxyl M MFN	4 + M[a]	RNA synthesis + Multi-site activity	Ridomil Gold/Copper 65W	F	114 MFN + 1362 CUZ g a.i./ha
			Ridomil Gold MZ 68WP	F	100 MFN + 1600 MCZ g a.i./ha
Metiram MTR	M	Multi-site activity	Polyram 80W	n/a	1600 g a.i. per 1000 L
			Polyram DF	n/a	1600 g a.i. per 1000 L

[a] The second group refers to the other active present in the formulation (see application rate).

[b] Mix type refers to formulated mixture (F) or tankmix (T)